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STUDIES ON HEMOGLOBIN REGENERATION IN PATIENTS WITH VITAMIN C DEFICIENCY*

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IN 1930, Mettier, Minot and Townsend[1] observed the occurrence of anemia in nine patients with clinical signs of scurvy, which was relieved by fruit, green vegetables and fresh liver, but in two cases was unrelieved by either iron or liver extract of the type effective in pernicious anemia. The remission of the anemia was attributed to the richness of these foods in vitamin C, and the conclusion was drawn that a specific anemia due to vitamin C deficiency probably existed. The subsequent isolation, crystallization and synthesis of vitamin C, the development of methods for its estimation and the realization that foods rich in vitamin C may be sources of iron, vitamin A and vitamin B complex, made it desirable that this concept be investigated further.

The available data in the literature are difficult to evaluate because of the lack of a control period in most cases, and because many observers have used orange juice rather than pure ascorbic acid. All the reported cases treated with orange juice showed beneficial effects on the anemia. In this category belong the clinical and experimental data of Mettier, Minot and Townsend,[1] Mettier and Chew,[2] Parsons and Hawksley[3] and Jennings and Glazebrook.[4] Besides vitamin C, orange juice is known to contain iron and vitamin A and vitamin B complex.[5] The suggestion has already been made that it may be necessary to explain the anemia of scurvy on the basis of deficiency of factors other than ascorbic acid.[6]

The data with respect to the effects of ascorbic acid are far less conclusive. Kenney and Rapoport[7] treated 5 anemic infants with scurvy. In none was there any control period. The anemia of 2 of the infants improved during vitamin C therapy alone. In the remaining 3, however, no improvement took place until iron was administered. Vaughan[8] has reported a scorbutic patient in whom it was apparently necessary to administer ascorbic acid to control the anemia. The peak of reticulocytosis occurred, however, on the third day following ascorbic acid administration, which makes one speculate as to whether this was too soon for a true causative relation. Croft and Snorf[6] could find no correlation between anemia and low vitamin C levels, nor did they get any reticulocytosis in 6 cases with "secondary anemia" and very low vitamin C levels by using synthetic vitamin C. Aron[9] reported the failure of response of the anemia of experimental scurvy to ascorbic acid administration but noted its successful treatment with germinated oats. Three cases of scurvy with anemia observed by Ungley[10] showed reticulocytosis and hemoglobin regeneration on a vitamin C free diet; a specific effect due to ascorbic acid administration could not be demonstrated. Dunlop and Scarborough[11] reported observations on 2 adults with scurvy in whom ascorbic acid apparently facilitated hemoglobin regeneration but produced no reticulocytosis.

The sporadic occurrence of a reticulocytosis without hemoglobin regeneration following ascorbic acid administration has been reported by Faulkner[12] and by Hall, Darling and Taylor.[13] Two of the scorbutic infants of Kenney and Rapoport[7] presented this phenomenon.

Indirect evidence bearing on this problem is presented by the work of Moore et al.[14] on the relation between serum iron and ascorbic acid levels. They have shown that administration of iron results in a decrease in plasma ascorbic acid concentration. The converse, however, is not true, and ascorbic acid administration has no apparent effect on serum iron levels.

It is therefore evident that the existing data concerning the necessity of ascorbic acid for the

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regeneration of hemoglobin are largely inconclusive. It is the purpose of this communication to report observations concerning hemoglobin regeneration in 5 patients with presumptive vitamin C deficiency and anemia, with particular reference to the necessity for ascorbic acid administration.

Methods

Five patients with presumptive vitamin C deficiency, as shown by complete chemical absence of reduced ascorbic acid from the blood plasma, were treated with bedrest and a diet limited to the following foods: whites of eggs, white bread, white soda crackers, butter, spaghetti, rice, bacon, corn syrup, tea, coffee and milk boiled for five minutes. None of these foods contain more than a trace of vitamin C or of vitamin B complex.

Three of the patients presented the clinical picture of scurvy, one pellagra, and the fifth idiopathic hypochromic anemia. All showed complete absence of reduced ascorbic acid from the blood plasma. Three patients had a moderate anemia, and in the others a mild anemia was rendered more severe by removal by venesection of 1600 cc. of blood.

Counts of the red and white cells, hematocrit determinations and hemoglobin estimations by a modification of the Klett–Summerson photoelectric-cell method[15] were made on venous blood every other day. Reticulocyte percentages were determined on capillary blood every day. Determinations of the plasma ascorbic acid by the methods of Mindlin and Butler[16] revised for the Klett–Summerson photoelectric colorimeter were made twice a week.

Abstracts of the case histories are as follows:

Case 1. A 49-year-old unemployed white man, who had lived alone and cooked his own meals for the last 3 years, subsisting on a diet markedly deficient in fruits and green vegetables, three weeks before admission developed ecchymoses over both legs and swollen, spongy, purple, protruding, painful gums that bled easily. Six years before entry, a diagnosis of tertiary syphilis had been made, and he had been given intensive specific therapy. There was no history of alcoholism. The tourniquet test was positive. Urine and stool examinations were negative. Gastric analysis showed normal acidity. A diagnosis of scurvy was made.

Case 2. A 55-year-old widower, who following the death of his wife lived alone for nine years, cooking his own meals and subsisting on a diet markedly deficient in fruits and green vegetables, seven weeks before admission developed large ecchymoses over both legs; three weeks later his gums became swollen and spongy and bled on the slightest trauma. There was no history of alcoholism. The tourniquet test was positive. Urine and stool examinations were negative. A blood Hinton test was positive. A diagnosis of scurvy was made.

Case 3. A 67-year-old white man with a 20-year history of postprandial distress and occasional tarry stools unrelieved permanently by appendectomy 20 years and gastroenterostomy 14 years previously, had subsisted for 5 years prior to entry on tea, white bread, milk, cream and coffee. Three months before admission he began to develop ecchymoses over both legs, and the postprandial distress recurred. The tourniquet test was positive. Urine examination was negative. A blood Hinton test was negative. Stool examination was markedly positive for occult blood. Gastric analysis showed normal acidity. X-ray examination of the stomach showed a small gastric ulcer and pyloric obstruction. Diagnoses of scurvy, gastric ulcer and pyloric obstruction were made.

Case 4. A 49-year-old single laborer for 2 years had consumed between a pint and a quart of whiskey daily and had eaten irregularly and inadequately. Two weeks before admission, following exposure to the sun, the backs of both his hands became red, swollen, painful and blistered. The tourniquet test was positive. The urine and stool examinations were negative. A blood Hinton test was negative. Diagnoses of alcoholic pellagra and subclinical scurvy were made.

Case 5. A 50-year-old housewife, subsisting on a diet slightly deficient in fruits and vegetables, complained of dysphagia of 5 years' duration and dysuria and dyspnea of 1 year's duration. She had had nine pregnancies. A marked hypochromic anemia was present. Examinations of the urine showed mild pyuria and bacilluria (colon bacillus). Stool examination was negative. A blood Hinton test was negative. Gastric analysis showed achylia. Diagnoses of chronic cystitis and idiopathic hypochromic anemia were made.

Results

A summary of the results is presented in Table 1. It will be observed that 4 of the 5 patients showed satisfactory hemoglobin regeneration without vitamin C administration, even though they were kept on a diet containing only traces of vitamin C and vitamin B complex. In 3 of these 4 patients, ascorbic acid, administered after the initial period of hemoglobin regeneration, neither caused reticulocytosis nor increased the speed of hemoglobin increase. The remaining patient had clinical scurvy associated with melena and anemia. During the control period, neither the melena nor the anemia disappeared. Coincident with the administration of vitamin C, the melena ceased, and reticulocytosis and hemoglobin regeneration ensued.

It is also of interest to note that in 2 patients (Cases 2 and 5) complete regeneration of hemoglobin did not occur until after they were placed on yeast and a general diet.

Discussion

The observations reported here confirm those of Ungley[10] and support the suggestion of Croft and Snorf that it is possible that synthetic vitamin C is not the antianemic factor in scorbutic anemia, and that the universal success with orange juice may be attributed to a factor other than reduced ascorbic acid. Since orange juice contains vitamin B

PERIOD OF OBSERVATION	DAYS	CASE 1			CASE 2			CASE 3			CASE 4			CASE 5		
		HEMOGLOBIN %	RETICULOCYTES %	PLASMA VITAMIN C mg./100 cc.	HEMOGLOBIN %	RETICULOCYTES %	PLASMA VITAMIN C mg./100 cc.	HEMOGLOBIN %	RETICULOCYTES %	PLASMA VITAMIN C mg./100 cc.	HEMOGLOBIN %	RETICULOCYTES %	PLASMA VITAMIN C mg./100 cc.	HEMOGLOBIN %	RETICULOCYTES %	PLASMA VITAMIN C mg./100 cc.
								Ferrous sulfate, 0.8 gm. daily, by mouth								
Control	0	45	10.0	0.0	71	1.4	0.0	58	2.6	0.0*	88	0.6	0.17	56	1.1	0.0
	2	51	12.8		76	2.0		64	1.8	0.0	98	0.5	0.0			
	4	53	11.7	0.0	74	1.4	0.0	65	1.6		100	0.6				
	6	61	8.9	0.0	74	1.0	0.0	60	2.5	0.0*	99	0.2	0.0	54	0.6	0.0
	8	68	4.5		74	1.1		63	2.1	0.0	95	0.4	0.0			
	10	64	2.4	0.0	79	1.0	0.0	65	1.6							
	12	67	3.5	0.0	82	0.5	0.0	60	0.9	0.0						
	14	71	3.7		79	0.5		56	2.3	0.0*				55	0.4	0.0
	16	71	1.4	0.0	84	0.5	0.0									
	18				84	0.6	0.0									
		Ascorbic acid, 0.4 gm. daily, by mouth			Venesection (1600 cc.); no therapy.			Ascorbic acid, 0.4 gm. daily, by mouth; ferrous sulfate, 0.8 gm. daily, by mouth.			Venesection (1670 cc.); ferrous sulfate, 0.4 gm. daily, by mouth.			Ferrous sulfate, 0.8 gm. daily, by mouth		
First	2	77	1.4	0.0	66	0.7	0.0	55	2.2	0.0	70	0.2		55	0.8	0.0
	4	78	1.2		65	2.0		57	1.8	0.83	71	0.8	0.0	59	2.6	0.0
	6	81	0.4	0.55	69	1.5		59	3.0	1.02	73	1.5	0.0	59	2.3	
	8	80	0.7		67	1.3	0.0	60	4.3		75	2.8		62	0.5	0.0
	10	79	0.4	1.11	69	0.6	0.0	64	4.0	0.74	71	1.5	0.0	60	1.6	0.0
	12	82	0.5		65	2.1		63	3.5	0.78	75	1.9	0.0	67	1.6	
	14	83	0.6	1.04	70	2.0	0.0	65	3.4		78	1.8		64	0.8	0.0
	16				69	2.3	0.0	69	1.5	0.96	81	1.2	0.0	67	1.0	0.0
	18							67	1.5	0.93	82	2.0	0.0	67	1.4	
	20							72	1.4		84	1.4				
	22							73	2.2	0.93	85	1.3	0.0			
	24							78	0.6	0.99	89	0.9	0.0			
	26							81	1.0							
	28							84	1.2	1.12						
					Ferrous sulfate, 0.8 gm. daily, by mouth									Ferrous sulfate, 0.8 gm. daily, by mouth; ascorbic acid, 0.4 gm. daily, by mouth.		
Second	2				73	2.0								64	1.0	0.45
	4				72	2.5	0.0							65	1.1	1.04
	6				71	1.6								66	0.5	
	8				70	1.3	0.0							66	0.5	1.46
	10				77	1.6	0.0							65	0.4	1.52
	12				78	2.1								65	0.8	
					Ascorbic acid, 0.4 gm. daily, by mouth									General diet; ferrous sulfate, 0.8 gm. daily, by mouth.		
Third	2				77	1.1	0.0									
	4				80	1.0	0.20							68	0.6	1.36
	6				80	0.6										
	8				77	0.6	0.63									
	10				78	0.8	0.75									
	12				73	0.9										
	14				76	0.4	0.87							72	0.9	1.55
					Ferrous sulfate, 0.8 gm. daily, by mouth; ascorbic acid, 0.2 gm. daily, by mouth; brewer's yeast tablets, 60 daily, by mouth.												
Fourth	2				73	0.8	0.71									
	4				75	0.8										
	6				78	1.6	0.75									
	8				78	0.9	0.82									
	10				80	0.6										
	12				83	0.6	0.58									
	14				86	0.9	0.51									

*Occult blood in stools.

complex, it is conceivable that one of the anti-anemic factors shown by Wills and Evans,[17] Miller and Rhoads,[18] and others,[19, 20] to be concerned in various experimental anemias may also be concerned in the anemia of scurvy. This speculation is particularly inviting because of the original report of Mettier, Minot and Townsend[1] that liver extract was not effective, whereas raw liver pulp was, which is exactly what Wills has found in tropical macrocytic anemia.

Crandon and Lund[21] have recently reported studies on a normal active adult on a vitamin C free diet receiving supplements of iron and every known vitamin except vitamin C for four months. During this period, despite blood loss of 2300 cc. by venesection for experimental reasons, the hemoglobin and red-cell count fell only slightly below their initial values and were quickly restored to normal levels by the ingestion of ferrous sulfate. During two additional months on the vitamin C free diet,[22] manifest scurvy developed, but in spite of blood loss by venesection of 2400 cc. more, neither the hemoglobin nor the red-cell count fell. Thus, in a normal man on a vitamin C free diet for six months, during which manifest scurvy developed, and in spite of blood loss by venesection totaling 4700 cc., no anemia developed. This is confirmatory of the conclusions drawn here.

It is necessary to comment on the significance of the chemical absence of ascorbic acid from the plasma, which has been taken here as presumptive evidence of considerable deficiency of this factor. This is in agreement with most authorities.[23] It must be borne in mind, however, that the absence of ascorbic acid from the plasma implies complete absence from neither the blood nor the tissues. This is clearly demonstrated by the recent work of Butler and Cushman.[24] It is therefore conceivable that the anemia that has been described as due to vitamin C deficiency may not occur until the body is completely depleted of this vitamin.

The role of blood loss in the development of the anemia accompanying scurvy is unsettled. Two facts seem to point to its significance. The first is that scurvy is essentially a hemorrhagic disorder and, in common with analogous conditions, might be expected to be accompanied by an iron-deficiency anemia. The other is the reticulocytosis that many patients with scurvy present on admission to the hospital. This phenomenon has been observed by Ungley[10] and Dunlop and Scarborough[11] and was presented by Cases 1 and 3 reported here. Added evidence that blood loss may be significant in the anemia accompanying scurvy is offered by Case 3. This patient had melena, which did not cease until ascorbic acid was administered; coincident with the cessation of blood loss, hemoglobin regeneration occurred.

Summary and Conclusions

Observations on regeneration of hemoglobin were made in 5 patients with moderate anemia and with presumptive vitamin C deficiency, as indicated by total absence of reduced ascorbic acid from the plasma. In 4 patients regeneration of hemoglobin took place spontaneously or in response to iron therapy alone. It is concluded that hemoglobin regeneration may occur in the absence of reduced ascorbic acid from the blood by chemical test.

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SULFANILAMIDE IN THE TREATMENT OF ACUTE PELVIC INFLAMMATORY DISEASE*

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THE striking results of sulfanilamide therapy in streptococcal infections and acute gonorrhea reported by numerous observers have led the members of the Gynecological and Obstetrical Service at the Boston City Hospital to extend the application of this drug to the treatment of acute pelvic inflammations. It would be superfluous to review the literature on sulfanilamide therapy. The list of papers on the use of sulfanilamide in streptococcal and gonococcal infections in women comprises over one hundred and fifty references. In marked contrast to this extensive literature, there is a paucity of evidence of the use of the drug in the common types of acute pelvic inflammation.

Gillette,[1] writing on the use of sulfanilamide in infections of the upper genital tract in women, reported a series of 50 cases. Of 16 patients with adnexal masses, 5 were improved, 6 showed no change and in 5 the masses increased in size in spite of the treatment. In 25 cases of recurrent salpingo-oöphoritis, 5 showed only "adnexal thickening," and of these 4 became afebrile in five days. In 8 cases with large inflammatory masses, there was no improvement. In 12 patients with small adnexal masses, there was some diminution in size in 5 and no change in 7. Gillette considered sulfanilamide therapy to be more effective during the initial attack than later.

Goff,[2] with a rather small experience, concluded that in patients seen during the first three days of gonorrheal pelvic infections the process could be aborted by sulfanilamide, but that in those seen later, when mass formation had occurred, improvement was much slower.

Manor,[3] in a study of gonorrheal infections of the lower genital tract, found that 36 per cent of the patients also had intrapelvic inflammatory disease. These showed some improvement after the use of sulfanilamide.

Barringer and her associates[4] noted that adnexal masses lost their tenderness and in some cases diminished in size under sulfanilamide therapy. Increased mobility of the uterus followed. According to their observations, 18 cases were improved, but 12 others showed no improvement.

Sulfanilamide therapy in acute pelvic inflammations has been carried on for more than a year on our gynecologic wards. We have thus been able to secure accurate data on 72 cases. To find out more definitely what benefit was derived from the use of sulfanilamide, an analysis has been made of 100 patients — as nearly as possible parallel to those who received sulfanilamide — who were treated during the presulfanilamide era by the routine of bedrest, fluids, catharsis, ice or heat to the abdomen and hot vaginal douches. It should be stated here that the patients who were given sulfanilamide received in all other ways the same treatment as the control series. We believed that a comparison of the results in these two series would give a clear idea of the value of sulfanilamide therapy in pelvic inflammatory disease. There were no fatalities in either series.

Although varying degrees of clinical severity appeared in different patients in each series, all presented the following characteristics: elevation of temperature to 101°F. or over, acute pain and tenderness, spasm or palpable masses — usually both — at the same or different periods of the process, leukocytosis and vaginal discharge. The majority of these attacks began either during or, more commonly, just after a menstrual period. One point that stands out very clearly in our observations is that recurrent attacks were on the average of shorter duration than the initial attack.

In the series not receiving sulfanilamide, the temperature fell to normal within one week after admission in 72 per cent. Since the other symptoms, such as pain, tenderness and leukocytosis improved almost parallel with the fall in temperature, it seems sufficiently accurate to accept the latter as the measure of improvement. This criterion, therefore, will be used throughout this paper.

The average duration of the febrile reaction in the control series was 6.7 days. The longest duration of temperature elevation in any case was 35 days. In 63 patients suffering from their first attack the average was 7.9 days; in 37 patients with recurrent attacks it was 4.8 days.

Having established a definite standard for comparison of results, we turn to the series treated with sulfanilamide. The routine doses of sulfanilamide administered to patients thus treated were as follows: 120 gr. a day for the first two days, then 90 gr. a day until a definite fall in temperature was noted. The dosage was then cut

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to 60 and later to 40 gr. daily, being omitted after forty-eight hours of normal temperature. Sodium bicarbonate was given with the sulfanilamide in proportions varying from 10 gr. of sodium bicarbonate to 30 gr. of sulfanilamide up to equal amounts of each.

Untoward effects were slight. All cases showed more or less cyanosis, but this was not regarded as a contraindication to continuing the drug. Vomiting occurred in some cases, but was not severe enough to interfere seriously with the treatment. The red-cell and white-cell counts were carefully followed, and the former were more seriously affected than the latter, but not uniformly.

It seems evident that the blood of certain patients is definitely susceptible to the action of sulfanilamide. Marked falls in the red-cell count were limited to a few patients who showed decreases of from 1,000,000 to 1,400,000. The majority showed very slight drops in red-cell count. A few actually showed an increase in red cells while they were under treatment with sulfanilamide, due no doubt to improvement in the general condition from rest and proper diet. In four patients showing marked falls in the red-cell count, transfusion and cessation of medication were deemed advisable.

The white-cell count always dropped in the sulfanilamide-treated patients, but in some it rose at the beginning of the treatment before the sulfanilamide had begun to act on either the corpuscles or the inflammatory process. In these cases, however, the white-cell count eventually dropped to a level lower than that at the beginning of treatment.

It was always difficult to tell how much of the decrease in white-cell count was due to the sulfanilamide and how much to the subsidence of the inflammatory process. In the series not treated with sulfanilamide the average drop was 5200, whereas in those treated with sulfanilamide it was 5500 — not a significant difference. In the sulfanilamide series the leukocyte count in 1 case fell to 2400 from an original level of 12,200; the blood cells were carefully checked by the staff of the Thorndike Memorial Laboratory, and no evidence of agranulocytosis or of abnormal relations between the different types of leukocytes was obtained. This patient later went through operation without incident.

Seventy-two per cent of the sulfanilamide-treated patients showed a normal temperature within one week, exactly the same percentage as that of the untreated cases. The average time taken to produce a normal temperature was 5.8 days, a little less than one day shorter than that in the untreated cases; this is hardly a striking difference. In primary attacks (44 patients) the temperature elevation averaged 6.0 days, whereas in recurrent attacks (28 patients) the average was 5.7 days. The longest run of temperature was thirty-six days. In this patient the red-cell count fell from 3,600,000 to 2,400,000, and the white-cell count from 26,400 to 12,500 after continuous sulfanilamide therapy for eighteen days. Sulfanilamide administration was stopped, and after three transfusions the red-cell count was raised to 3,900,000; the patient ultimately recovered after developing a pelvic abscess that broke through into the rectum just as she was being prepared for colpotomy. In 1 case a pelvic abscess that formed while the patient was under sulfanilamide treatment was drained by colpotomy on the seventh day after admission; the temperature fell to normal two days later. These 2 cases must be regarded as absolute failures of sulfanilamide therapy.

Another question was whether or not sulfanilamide reduced in any way the number of patients ultimately requiring operation. Of course such statistics are somewhat influenced by the judgment of different operators. Thirteen per cent of the untreated series and 11 per cent of those who had received sulfanilamide were deemed to require salpingectomy. Abscess formation requiring vaginal drainage has already been referred to. In the sulfanilamide-treated series colpotomy was done on 3 of 72 patients, and in the untreated series on 4 of 100, the percentages being identical.

Summary and Conclusions

Seventy-two cases of acute pelvic inflammatory disease were treated with sulfanilamide. For purposes of comparison a careful analysis was made of 100 cases of acute pelvic inflammation treated in exactly the same way except that no sulfanilamide was given.

The dramatic results often obtained by sulfanilamide in streptococcal infections and by sulfanilamide and sulfapyridine in pneumonias were disappointingly absent.

The figures show that very little advantage was obtained by the administration of sulfanilamide. It is fair to state, however, that nearly all these patients had been ill at home for a considerable period before entering the hospital. It has been claimed, and may still be true, that sulfanilamide given in gonorrheal infections may prevent the development of tubal involvement; the drug is of little value, however, once the inflammatory process in the adnexa has become well established. Better results might be obtained if it were possible

to get these patients under treatment during the first twenty-four hours of the attack.

With careful blood checking no serious ill effects were experienced from the treatment. Marked damage to the red corpuscles appears to occur only in certain susceptible persons. The drop in the white-cell count is due more to subsidence of the inflammatory reaction than to the destructive effect of the drug on the white corpuscles.

The administration of sulfanilamide in acute pelvic inflammatory disease has not given notably better results than the former general and local methods of treatment.

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SPINAL ANESTHESIA IN OBSTETRICS, USING PONTOCAINE-GLUCOSE SOLUTION*

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SPINAL anesthesia, which has found wide applicability for surgical procedures on the abdomen and lower extremities, has not been fully appreciated in obstetrics. Perhaps the reason for this is the effort of a few obstetricians who persist in the belief that spinal anesthesia is dangerous.[1, 2] Reports of successful use of spinal anesthesia coming from different parts of the country do not bear this out, and our experience at the Boston City Hospital leads us to believe that spinal anesthesia is safe if a few simple rules are followed, and that it is very useful for the delivery of selected cases.

The first record of the use of spinal anesthesia in obstetrics is that of Babcock,[3] who reported a series of 53 cases, all operative. He made the observation that the uterine contractions continue after spinal anesthesia but, being without the normal aid of the voluntary expulsive forces, are inefficient even when supplemented by the associated relaxation of the pelvic outlet.

Cooke[4] in 1923, reported a series of 25 cases, of which 6 delivered spontaneously. In 1927 Cosgrove[5–10] wrote the first of several papers on the subject. On December 31, 1939, his series had grown to include 4880 cases (personal communication), and his papers contain a large amount of data on the subject. He reports 2 deaths, one in a case delivered from below, the other in a case of ruptured ectopic pregnancy.

Stollenwerck[11] reported 140 cases. Pitkin and McCormack[12] reported a series of 89 cases delivered from below and 65 cesarean sections without accident. Fraser[13] reported 64 cases delivered in the course of eight years. We have delivered 150 cases and have done 23 cesarean sections under spinal anesthesia. These make an incomplete but impressive total of 5425 deliveries.

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Technic

We have deviated somewhat from the usual method of spinal anesthesia used in obstetrics. Instead of 50 mg. of novocain crystals dissolved in spinal fluid, we have selected the combination of Pontocaine and 10 per cent glucose, as reported by Sise[14] and others, because of its heavy specific gravity. This solution is injected in the third or fourth lumbar space using a No. 20 to 22 spinal needle, with the patient in the sitting position. With the patient sitting up, the specific gravity of the solution prevents its sudden ascent in the spinal canal when there is a rise of 100 to 250 mm. in spinal-fluid pressure during a uterine contraction. One cubic centimeter of 1 per cent procaine and 5 per cent ephedrine sulfate is used to infiltrate the skin. The injection is made between contractions, very slowly and with no barbotage. After the injection the patient is permitted to recline, but a pillow is always placed under the head to make certain that a dangerously high anesthesia is not produced.

We use a very small dose: 5 mg. of Pontocaine (0.5 cc. of a 1 per cent solution, well mixed with 1 cc. of 10 per cent glucose). Large doses have no advantage in anesthesia, and the only patient who gave us anxiety had been given 15 mg. of Pontocaine. Although small doses are safe and satisfactory, large doses may be dangerous. The blood pressure and pulse rate are recorded every fifteen minutes.

The time of administration is a matter of judg-

ment. As will be discussed later, we agree with Cosgrove[7] that spinal anesthesia is satisfactory only as an anesthetic for delivery and is not useful as an analgesic during the first or second stage of labor. We try to time the administration in multiparas at full dilatation, with the presenting part in the mid-pelvis or lower mid-pelvis, and in primiparas with the cervix fully dilated and the head low, or otherwise at the time of decision to intervene.

The most satisfactory level of anesthesia extends to the tenth thoracic segment, or just below the umbilicus, for uterine pain from contractions is completely abolished when this level is reached. Anesthesia to the second lumbar segment is sufficient for a low-forceps operation with episiotomy, although the patient is conscious of uterine pain of diminished intensity. The delivery may be postponed for about fifty minutes after the spinal injection, with no effect on the fetus. Usually in sixty to seventy-five minutes, contractions again become painful. However, the anesthesia to the perineum permits repair of lacerations without discomfort for about two hours.

In cesarean sections we use 8 to 12 mg. of Pontocaine (0.8 to 1.2 cc. of a 1 per cent solution and 1.5 cc. of glucose). Usually a sufficiently high level of anesthesia is obtained with the patient in the horizontal position. If the anesthesia has not risen sufficiently high in five minutes, the patient may be placed in a moderate Trendelenburg position for a few minutes. Ordinarily the patient is not placed in Trendelenburg for ten minutes after the injection, and usually not until the abdomen has been opened.

Results

Deliveries from Below

In a period of three months, during which 750 cases were delivered at the Boston City Hospital, 150 patients were delivered from below under spinal anesthesia. This method was usually used in patients in whom an operative delivery was anticipated, and was routinely used for patients with a history of cough, for those with eclampsia, toxemia or heart disease and for those who had recently eaten. There were no maternal deaths and no stillbirths.

Supplementary anesthesia was required in 5 cases. In 4 of these the spinal anesthetic had been given too soon, so that the anesthesia had worn off before delivery could be safely effected. Three were among the first 8 patients on whom spinal anesthesia was tried. The fifth patient had no skin anesthesia, although uterine pain was abolished. In 2 additional cases, the anesthesia did not take effect, but a second injection produced a satisfactory result. In 2 patients not included in the series, we were unable to get into the subarachnoid space. We found, therefore, that the anesthesia was effective in 145 of 152 cases, or 95 per cent. The relatively high incidence of successful anesthesia, in addition to the simplicity of the method, is the chief argument for the choice of spinal over sacral anesthesia.

In two cases not previously mentioned, the anesthesia was repeated because of early administration of the first injection. The second anesthesia was found to last about thirty minutes longer than the first, with no apparent harm to the patient.

The types of delivery are listed in Table 1. Six of the mid-forceps deliveries were done because the anesthetic had been given too soon; if the anesthesia had been postponed, low-forceps or normal deliveries would probably have resulted. This error was made early in the series, and we believe that it is a matter of judgment in timing the administration. The conversion of a frank breech to a double footling was found to be difficult under spinal anesthesia, because of lack of uterine relaxation, and it was consequently attempted in only 1 case. For the same reason, version was not attempted under spinal anesthesia.

Table 1. *Types of Delivery.*

Delivery	Primiparas	Multiparas	Total
Normal	12	15	27
Low-forceps	91	12	103
Mid-forceps	12	0	12
Breech extraction	0	1	1
Footling extraction	1	1	2
Version	0	0	0
Scanzoni	5	0	5
Totals	121	29	150

The youngest patient was sixteen years of age, the oldest forty-one. One hundred and seventeen of the patients were twenty-five years old or under. Two had eclampsia, and were delivered by low forceps of living babies; both were well when discharged. Included in the series were 4 cases of pre-eclampsia, 1 of severe, though compensated, rheumatic heart disease, 1 of mild rheumatic heart disease, 1 of severe bronchitis, 1 of asthma and 1 of pyelitis. Several patients were suspected of having pulmonary tuberculosis, but in no case was the diagnosis verified by x-ray.

In 129 cases the level of anesthesia was between the eleventh and fifth thoracic segments; in 10 cases it was above this, and in 9 cases below. In 1 case there was no dermal anesthesia, and in 1 the anesthesia was at the tenth thoracic segment on the right and the first lumbar on the left. One patient had anesthesia to the chin for a short time a half hour after the injection, but felt perfectly comfortable and had no drop in blood pressure.

There was a fall in blood pressure of 20 mm. or more of mercury following spinal anesthesia in 29 of the 150 cases. We believe that many of these were due to the relief from the bearing-down pains rather than to a change in the vascular bed. Fall to a critical level was noted in only 1 case, already mentioned, in which a large dose of Pontocaine had been used. Three minims of a 1:1000 solution of adrenalin hydrochloride intravenously was promptly effective in restoring the blood pressure and the patient's feeling of well-being.

A poorly acting post-partum fundus was noted in 8 cases; usually the uterus contracted well. The placenta was retained in 3 cases. Manual extraction of the placenta was found to be difficult in the 2 cases in which it was done.

Of the late complications encountered, headache was the most frequent. There were 5 severe headaches and 21 slight headaches, none lasting over six days. This is a percentage of 17 and agrees almost exactly with that of Cosgrove.[10] This symptom is not nearly so frequently encountered in general surgical operations, and only 1 of 23 patients with cesarean section had a transitory headache. It seems, therefore, as Cosgrove[8] suggested, that the changes of spinal-fluid pressure accompanying labor may be a causative factor. Treatment consisted in keeping the patient flat, applying an ice bag to the head and administering codeine and aspirin.

For twenty-four hours two patients had difficulty voiding. There were no pulmonary complications. One prolonged anesthesia of the leg and temporary paresis of the leg muscles following a Scanzoni manipulation was thought to be traumatic obstetric paralysis rather than a result of spinal anesthesia.

Cesarean Sections

During a period of six months 26 of a total of 38 cesarean sections were attempted under spinal anesthesia. In 2 cases the lumbar puncture was unsuccessful, and in 1 case only a saddle type of anesthesia was obtained so that a nitrous oxide-oxygen-ether anesthesia had to be used. The anesthesia was therefore satisfactory in 88 per cent of this small series. In 1 case the patient developed an extreme pruritus after medication, which caused so much restlessness that it was necessary to supplement the anesthesia with nitrous oxide after the delivery of the placenta.

In 22 cases a transverse cervical section was done, and in 1 a Porro.

There was an appreciable blood-pressure drop in only 2 patients, both of whom were operated on for bleeding from placenta previa. The blood pressures fell momentarily to 80 systolic, 58 diastolic, and 64 systolic, 40 diastolic, respectively; neither case required extreme measures at the moment, but their course suggests that this may not be the best anesthesia for cases with bleeding.

Two cases were in labor. No difficulty was experienced in the extraction of the infant, although uterine contractions could be perceived.

Convalescence was uniformly satisfactory. There were no respiratory complications. There were no deaths and no stillbirths.

The advantages of spinal anesthesia for cesarean section seem to be complete relaxation of the lower abdominal musculature, the absence of any depressing effect on the fetus, and the exceptionally satisfactory convalescence.

Discussion

Advantages and Disadvantages

We believe that spinal anesthesia should be used in patients with toxemia, eclampsia or nephritis; acute or chronic pulmonary conditions; upper respiratory infections; diabetes; and a full stomach. The anesthesia is also useful as a way of delaying labor without injury to the infant. For example, spinal anesthesia was to be used in the delivery of a private case, a multipara, because of a cough of six weeks' duration. Progress in the late first stage was unexpectedly rapid; although the obstetrician could not reach the patient within a reasonable time, spinal anesthesia permitted his delivery of the baby forty-five minutes later with no complications to mother or baby. Another feature of the anesthesia is that the patient may have the thrill of hearing her baby's first cry while having a painless delivery.

The absence of any narcotizing effect on the baby has made it possible to use morphine as a sedative in combination with Seconal and Sodium Amytal, with no marked depressant effect on the baby. Using 3 gr. of Seconal and 6 to 9 gr. of Sodium Amytal, with 1/6 gr. of morphine, we have noted a quiet restful analgesia that is in marked contrast with the analgesia dependent on scopolamine. Cosgrove[7] first suggested that morphine might be safely used during delivery in combination with spinal anesthesia.

Relaxation of the vagina and the perineum is sometimes quite marked, and is a definite advantage. Tightness of the skin and fascia is still present, however, and the incidence of episiotomies was not greatly reduced in our cases — in the delivery of 121 primiparas there were episiotomies in 73 and second-degree lacerations in 5.

Any intrauterine manipulation is more difficult under spinal anesthesia. Although we attempted no versions, we disagree strongly with Pitkin,[15] who advocates the use of large doses of a spinal anesthetic to relax the uterus for the performance

of version. Large doses may be dangerous, and the tone of the uterus is sufficiently great to make the procedure difficult, if not hazardous.

A further disadvantage is the increased incidence of forceps deliveries. To ensure a normal or low-forceps delivery, we advocate waiting for the head to come well into sight, if possible, in primiparas before administration of the anesthetic.

Physiologic Aspects

Three interesting observations concerning the physiology of labor have been brought to light by these studies, namely, the nerve pain paths associated with labor, the effect of spinal anesthesia on the cervix and the effect of spinal anesthesia on the rate, force and duration of uterine contractions.

Cleland[16] has demonstrated experimentally that pain accompanying childbirth is a combination of a deep uterine pain, which can be blocked by anesthetizing the eleventh and twelfth thoracic segments on both sides, and a pain from the genital tract which can be blocked by anesthetizing certain sacral roots. We have been able to confirm this in part by noting the effect on uterine pain of spinal anesthesia to different skin levels. There is complete relief from uterine pain when the anesthesia is an inch below the umbilicus or above this level. However, if a lower level of anesthesia is obtained, there is some pain with each contraction, but this pain is of diminished intensity. In the case in which the anesthesia level extended to the tenth thoracic segment on the right side and to the first lumbar on the left, the patient complained of left-sided uterine pain. If the sacral area alone is blocked, the patient notes a diminution of intensity of labor pain; it therefore seems that some of the pain fibers must enter by the sacral and lumbar roots as well as by the eleventh and twelfth thoracic roots.

We were particularly interested in the possibilities of the relaxing effect of spinal anesthesia on the cervix. In the French literature much is written concerning the rapid termination of pregnancy at term by using spinal anesthesia, a method originated by Delmas.[17] To study the effect of spinal anesthesia on the cervix, two multiparous toxemic patients, who were to have their membranes ruptured for the induction of labor, were selected. Spinal anesthesia was administered, and a gentle digital invasion of the cervix was made. This demonstrated in both cases that there is no ready relaxation of the cervix secondary to the spinal anesthesia. Similarly in a patient whose cervix had been well effaced by labor, but was dilated to admit only two and a half fingers, vaginal examination with spinal anesthesia showed the cervix to be no more dilatable than without anesthesia. It is suggested, therefore, that spinal anesthesia is not an adjunct to *accouchement forcé*.

The third interesting aspect of spinal anesthesia is that uterine contractions continue. This is partly due to the fact that sympathetic fibers from higher in the spinal cord are not blocked, because they descend in the lateral sympathetic trunks.

That the uterus does contract painlessly under spinal anesthesia can be demonstrated by palpating the abdomen. Likewise, at cesarean section under spinal anesthesia on a patient in labor, we have actually observed uterine contractions, as has Cosgrove.[9] Pressure measurements can be made with a hydrostatic bag inserted into the uterus while the membranes are still intact, and then connecting the bag by a water-filled tube to a mercury manometer. Cosgrove[9] reports such an experiment and states that there was no essential change in the power of contractions. However, Bourne and Burn[18] performed a similar experiment using Stovaine as the anesthetic, and showed that contractions continued irregularly, but that the uterus did not relax to the same degree between contractions. They concluded that this contraction of the lower segment would slow labor if spinal anesthesia were given early, but would hasten labor if it were given at full dilatation. We have repeated this experiment, and our results did not completely corroborate either of the above observations. Following anesthesia the contractions that had been at regular intervals and of equal intensity and duration became irregular in time, in strength of contraction and in duration. There was no cessation of contractions during the first ten minutes, as is sometimes reported. The base line in our experience remained the same: about 40 mm. of mercury. This indicates a less effective type of labor, which in addition to the loss of voluntary muscle contraction in spinal anesthesia has the effect of checking the progress of labor.

Summary and Conclusions

Small doses of Pontocaine, combined with 10 per cent glucose, are recommended for spinal anesthesia in selected obstetric cases, including patients with toxemia, eclampsia or nephritis, with acute or chronic pulmonary infections, with upper respiratory infections or with diabetes and those who have recently eaten. Uterine pain is abolished if the anesthesia reaches above the level of the eleventh thoracic segment. Under this type of anesthesia, uterine contractions continue, although they become irregular, less powerful and of shorter duration; hence, the progress of labor is delayed, and intrauterine manipulation is contraindicated. It has no effect on the dilatability of the cervix.

Pontocaine-glucose anesthesia was used for the delivery of 150 patients from below and for cesarean section in 23 patients. There were no stillbirths or maternal deaths. The only distressing complication was headache, which occurred in 17 per cent of the patients delivered from below and persisted for as long as six days.

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DIABETES MELLITUS AND PREGNANCY

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THE development of pregnancy in a diabetic woman was a rarity before the discovery of insulin. The cause of the diminished fertility is the severe regressive changes of the ovaries, which manifest themselves in the disappearance of the primordial follicles, with a deficient maturity of the follicles and the lutein bodies. The hypophysis also shows changes from the normal: its weight is decreased and the eosinophilic cells are reduced in number. The basophilic cells show hydropic degeneration. The theory has therefore been proposed that the atrophy of the follicles is due to a decreased function of the hypophysis, namely, a diminished effect of its gonadotropic hormone.[1] In the past, actually only about 5 per cent of all diabetic women became pregnant.

Since the discovery of insulin and its introduction in the treatment of diabetes mellitus, the fertility of diabetic women has distinctly increased and cases of pregnancy and diabetes are observed much more frequently. Therefore, the question of the fate of diabetic pregnant women and the children of diabetic mothers has become considerably more significant.[2] The mortality was about 45 per cent before the introduction of insulin. It has decreased considerably since then. Nevertheless, it is still estimated as 10 to 17 per cent.[2-5] I can share neither the optimism of some observers nor the pessimism of Bertram,[6] who states that only in mild cases of diabetes without significant rise of the blood sugar and without tendency to acidosis should one allow the pregnancy to continue. According to him, every pregnancy should be interrupted with the first sign of metabolic changes, since no one can foresee the outcome for either mother or child. According to Duncan and Fetter,[7] the need of insulin rises in the first trimester of pregnancy, remains constant in the second trimester, becomes greater in the third and suddenly decreases again after delivery. In my experience, the influence of pregnancy on the diabetic patient is not always the same and cannot be predetermined in any particular case. I have seen diabetic women in whom severe diabetes remained almost constantly unchanged during the whole pregnancy. On the other hand, some pregnant women with mild diabetes suddenly became worse without a demonstrable cause, and rapidly developed coma and died.

Diabetes is even more unfavorable for the unborn child than for the mother. In this regard insulin cannot accomplish much. Before its introduction approximately 60 per cent of such children either were stillborn or died within a few days. Since its introduction the mortality is still about 45 per cent.[1, 8] There are apparently three causes for this failure. The first is because the fetus is often overweight and abnormally large. Bix[9] found giant infants in 20 per cent of diabetic fetuses, but in only 3 per cent of normal ones. Of 608 children of 155 diabetic mothers, 385 were overweight, 110 had a weight of 4 kg. (8 lb., 13 oz.), 47 of 4.5 kg. (9 lb., 14 oz.), 49 of 5 kg. (11

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lb.) and 17 of greater than 5 kg. (11 lb.). Because of the mother's condition or that of the child, rapid delivery may become necessary and may result in birth injury, at times leading to the death of the child. Secondly, these children may die without any demonstrable cause. And, finally, abortion, miscarriage, and stillbirth are frequent. Children with congenital diabetes, however, are extremely rare; Joslin[10] knows of only 3 such cases.

In attempting to account for the high mortality in the children of diabetic mothers, one finds that the greatest danger exists during delivery, which even when normal may cause considerable injury, especially to the blood vessels. All endeavors to deliver such children alive and keep them so must take this factor into account, and avoid even the most insignificant birth injuries. Nothmann and Hermstein[11] were the first to recommend prophylactic cesarean section to preserve the life of these children. Others followed.[12–22] In my experience it has resulted in a marked lowering of the mortality, as shown in the 5 cases reported below. At the same time, investigations were made to determine how the mother and fetus influence each other in regard to carbohydrate metabolism.

Case 1. A 32-year-old woman, with a history of diabetes of 5 years' duration, was admitted to the hospital on February 6, 1930, in diabetic coma, in the 5th month of her first pregnancy. There was no family history of diabetes. In January the glycosuria had increased considerably, and on February 1 the patient began to feel extremely weak. Severe palpitation of the heart appeared, accompanied by dyspnea and pains in the back and the abdomen.

After the patient had regained consciousness in the hospital labor set in, and the pregnancy was interrupted. The fetus was dead. On February 11, she was transferred to the medical clinic, where she remained until March 15.

Table 1. *Summary of the Carbohydrate Metabolism of Case 1 during the Last Month of Pregnancy.*

Date	Amount of Urine	Urine Sugar	Blood Sugar	Diet	Insulin
	cc.	*gm.*	*mg./100 cc.*	*gm.*	*units*
3/30	1200	2.4	232	C.H. 129 P. 44 F. 70	110
4/2	1100	0.6	217	C.H. 140	100
4/5	950	0.8	208	C.H. 140	80
4/15	1400	0.0	197	C.H. 140	70
4/22	1350	0.6	190	C.H. 161	70
4/27	1600	2.8	194	C.H. 189	70
4/28	1750	1.4	185	C.H. 189	70
4/29	1450	0.0	160	C.H. 189	70
4/30	1500	0.2	155	C.H. 189	70
5/1	1100	0.0	140	C.H. 189	70
5/2	1450	0.0	145	C.H. 189	70

The urine was sugar-free on a diet of 48 gm. of protein, 70 gm. of fat and 140 gm. of carbohydrates, with 20 units of insulin twice a day.

After discharge from the hospital the patient followed orders strictly and remained under medical control; the urine was examined daily. With the beginning of a second pregnancy in September, 1931, the glycosuria again increased, and the dosage of insulin had to be gradually increased to 110 units to keep the patient sugar free on the same diet. In the 8th month of pregnancy she was readmitted to the hospital and remained there until after delivery. During the last month of pregnancy a considerable amelioration of the diabetes occurred, as shown in Table 1. To avoid hypoglycemic reactions a slight glycosuria was permitted. The amount of insulin was diminished considerably, and the carbohydrate intake was increased. On May 3, 1932, the patient was transferred to the obstetric department, where during the afternoon labor started. On May 4 she was delivered by cesarean section under spinal anesthesia; the baby was delivered in 10 minutes, and the entire operation lasted 15 minutes. The child, a boy, weighed 9 pounds, 14 ounces. Table 2 shows the blood sugar of the mother during the last 2 days of pregnancy. During the early part of labor there was a gradual rise of the blood sugar from 142 to 208 mg. per 100 cc. The blood cholesterol was 224 mg. Two hours before delivery the blood sugar was 200 mg., half an hour before 121 mg., at the time of delivery 118 mg. and at the end of the operation 110 mg., the patient having received an additional amount of insulin (20 units) half an hour before delivery. The sugar content of the amniotic fluid was 108 mg., that of the umbilical vein 94 mg. and that of the umbilical artery 82 mg. The blood cholesterol content of the umbilical vein was 85 mg., and that of the umbilical artery 73 mg.

Table 2. *Blood Sugar of Case 1 during Delivery.*

Date	Time	Blood Sugar	Insulin	Remarks
		mg./100 cc.	*units*	
5/3	7:00 a.m.	140	25	
	12:00	142	25	
	3:00 p.m.			Weak labor
	6:00	150	20	
	9:00	160		
5/4	7:00 a.m.	208	25	
	7:20			Weak labor
	10:00	200	20	
	11:00		20	
	11:20	121		
	12:00			Beginning of operation
	12:10 p.m.	118		Birth
	12:15	110		End of operation
	3:00	134		

Table 3. *Summary of the Carbohydrate Metabolism of Case 1 during the First Two Weeks after Delivery.*

Date	Amount of Urine	Urine Sugar	Blood Sugar	Diet	Insulin
	cc.	*gm.*	*mg./100 cc.*	*gm.*	*units*
5/7	1500	15.0	294	C.H. 171 F. 70 P. 48	70
5/8	1700	31.2	310	C.H. 171	70
5/10	1400	12.6	310	C.H. 171	80
5/13	1300	4.2	241	C.H. 171	80
5/18	1800	4.8	221	C.H. 171	80
5/19	1500	0.0	185	C.H. 171	80
5/20	1600	0.0	149	C.H. 171	60
5/21	1250	0.0	130	C.H. 171	50
5/22	2100	0.0	154	C.H. 171	45

The abdominal incision healed very quickly. In the first few days the baby was put on the mother's breast. On the 14th day the milk dried up and the child, who was thriving, was transferred to the children's department for further care. After delivery the mother's sugar tolerance

became worse, as compared with that of the last weeks of pregnancy, but improved quickly in 2 weeks' time (Table 3).

Of special significance were the results of the examination of the baby's blood sugar in the first days after birth: for 4 days it showed a tendency toward hypoglycemic

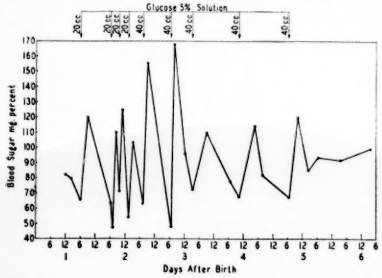

FIGURE 1. *Blood Sugar of the Baby in Case 1 during the First Days after Birth.*

values. During this time there was transient unconsciousness on the 2nd day after the birth, when the blood sugar was 45 mg. per 100 cc. Only temporarily could it be elevated by injections of glucose. After the 5th day it remained normal (85 mg.) (Figure 1).

CASE 2. The patient was a 29-year-old woman who had suffered from severe diabetes for 6 years. During her married life of 6 years, she had two stillbirths, and the third child had died 2 days after delivery from a cephalhematoma resulting from a birth injury. Her longing for a living child induced me to recommend prophylactic cesarean section. When the patient became pregnant she resolved to follow this advice. In the early months of pregnancy her sugar tolerance decreased. Having been sugar free before she became pregnant on a diet of 64 gm. of protein, 140 gm. of fat and 120 gm. of carbohydrate, with 50 units of insulin daily, she excreted 30 to 40 gm. of sugar in the urine daily. The dosage of insulin had to be increased to 70 units daily, upon which the glycosuria was decreased to 3 to 5 gm. daily. To avoid a hypoglycemic reaction the insulin was not further increased. In the 7th month of pregnancy clinical examination demonstrated no changes in the sugar tolerance.

At the end of the 8th month of pregnancy the patient was readmitted to the medical clinic. She had felt labor pains the day before. Large amounts of acetone bodies were found in the urine, also 30 to 40 gm. of sugar. The patient was therefore transferred to the obstetric clinic and delivered by cesarean section. The baby, a boy, weighed 7 pounds, 1 ounce, and remained alive. The blood sugar taken during the operation was 132 mg. per 100 cc. At the end of the operation it was 120 mg. and the blood cholesterol was 214 mg. The sugar value of the amniotic fluid was 104 mg., that of the umbilical vein 98 mg. and that of the umbilical artery 86 mg. The cholesterol in the umbilical vein was 78 mg. and that in the umbilical artery 58 mg.

The baby was breast-fed for 18 days, when the mother became ill with mastitis. The milk dried up several days later. After delivery and during lactation a considerable improvement in sugar tolerance was noted in the mother. On a diet of 66 gm. of protein, 155 gm. of fat and 150 gm. of carbohydrate, with 60 units of insulin daily, she was sugar free. The fasting blood sugar was 188 mg. The baby's blood sugar showed a tendency to hypoglycemia for 5 days (Table 4), and was only temporarily increased by injections of glucose.

CASE 3. The patient was a 24-year-old primipara who had suffered from diabetes for 2 years. She had had only dietetic treatment. In the 8th month of pregnancy large amounts of ketone bodies were found in the urine without a demonstrable cause. On admission to the medical clinic the blood sugar was 286 mg. per 100 cc.; 1.25 gm. of acetone and 6.64 gm. of oxybutyric acid per 100 cc. were found in the urine, and 0.15 gm. of acetone and 0.69 gm. of oxybutyric acid in the blood. A living child was delivered

TABLE 4. *Blood Sugar of the Baby in Case 2 for Several Days after Birth.*

DATE	TIME	BLOOD SUGAR	TREATMENT
		mg./100 cc.	
6/2	1:30 p.m.	86 (umbilical artery)	
	4:00	82	
	8:00	68	
	8:30		20 cc. 5% glucose, subcutaneously
6/3	6:30 a.m.	72	
	9:30	54	
	10:00		40 cc. 5% glucose, subcutaneously
	11:00	136	
	4:00 p.m.	102	
	8:00	76	
	8:30		40 cc. 5% glucose, subcutaneously
6/4	6:30 a.m.	84	
	10:00	74	
	10:30		40 cc. 5% glucose, subcutaneously
	2:00 p.m.	102	
	6:00	76	
	9:00	48	
	9:30		40 cc. 5% glucose, subcutaneously
6/5	6:30 a.m.	98	
	10:00	92	
	2:00 p.m.	82	
	6:00	68	
	6:30		40 cc. 5% glucose, subcutaneously
6/6	6:30 a.m.	78	
	10:30		20 cc. 5% glucose, subcutaneously
	12:00	134	
	6:00 p.m.	85	
	9:00	78	
	9:30		20 cc. 5% glucose, subcutaneously
6/7	6:30 a.m.	94	
	10:00	85	
	2:00 p.m.	82	
	6:00	85	
6/8	6:30 a.m.	92	
	12:00	85	
	8:00 p.m.	98	
6/9	6:30 a.m.	96	
	2:00 p.m.	92	

by prophylactic cesarean section; the baby, born in the middle of the 8th month, weighed 5 pounds, 5 ounces. The blood sugar of the mother at the end of the confinement was 124 milligrams per 100 cc.; the sugar of the amniotic fluid was 110 mg., that in the umbilical vein 92 mg. and that in the umbilical artery 82 mg. The mother's blood cholesterol was 302 mg. per 100 cc. Tables 5 and 6 demonstrate the values of the blood sugar of the mother during the confinement, and of the baby for several days after delivery.

The patient recovered very quickly after the operation. The breast feeding had to be stopped after a few days because of lack of milk. The diabetes improved rapidly after delivery. Fourteen days after delivery, 10 units of insulin was needed daily. A week later the injection of insulin was stopped.

The baby developed icterus neonatorum 2 days after birth; this disappeared 8 days later. Table 7 shows the cholesterol values from the birth until the recovery from the jaundice.

Case 4. The patient was a 32-year-old woman with severe diabetes of 7 years' duration. Four years previously a precomatose condition had developed. She had married

Table 5. *Blood Sugar of Case 3 during Delivery.*

Date	Time	Blood Sugar	Insulin	Remarks
		mg./100 cc.	*units*	
3/4	12:30 p.m.	286		
	1:30		30	
	4:00	225		
	6:00	210	20	
	8:00	192		
3/5	6:30 a.m.	210	20	
	9:00	176	10	
	11:00	135		
	11:30		10	Beginning of operation
	11:50			Birth
	11:58	124		End of operation
	2:00 p.m.	132		
	2:30		10	
	6:00	102		

3 years previously and had given birth to a stillborn child a year later. She was admitted to the clinic during the 8th month of her second pregnancy. The baby was delivered by prophylactic cesarean section and weighed 5 pounds, 5 ounces. The 2nd, 3rd and 4th days after birth

Table 6. *Blood Sugar of the Baby in Case 3 for Several Days after Birth.*

Date	Time	Blood Sugar	Treatment
		mg./100 cc.	
3/5	11:00 a.m.	82 (umbilical artery)	
	2:00 p.m.	68	
	2:30		20 cc. 5% glucose, subcutaneously
	4:00	128	
	8:00	111	
3/6	7:30 a.m.	72	
	10:00	58	
	10:30		20 cc. 5% glucose, subcutaneously
	12:00	132	
	4:00 p.m.	69	
	4:30		20 cc. 5% glucose, subcutaneously
3/7	8:00 a.m.	78	
	8:30		20 cc. 5% glucose, subcutaneously
	12:00	104	
	6:00 p.m.	72	
	6:30		20 cc. 5% glucose, subcutaneously
3/8	8:00 a.m.	116	
	12:00	102	
	4:00 p.m.	96	
3/9	8:00 a.m.	102	

the child had spells of unconsciousness, which were promptly relieved by injections of glucose. The blood sugar on the 2nd day of life during an attack of unconsciousness was 43 mg. per 100 cc. The blood cholesterol was 66 mg. Detailed investigations of the metabolism could not be made.

Case 5. The patient was a 28-year-old woman who had had diabetes since the age of 18. She married at 24 and at 26 had a miscarriage. She was delivered by prophylactic cesarean section in the ninth month of pregnancy. The child, a girl, weighing 5 pounds, 10 ounces, sank into transient unconsciousness on the 3rd and 5th days after delivery. In this case also, injections of glucose were given with quick response. The blood sugar of the mother during labor, 1 hour after the injection of 15 units of insulin, was 125 mg. per 100 cc. The sugar of the amniotic fluid was 98 mg., the blood sugar in the umbilical vein

Table 7. *Blood Cholesterol of the Baby in Case 3.*

Date	Blood Cholesterol
	mg./100 cc.
3/5	162 (umbilical artery)
	130 (umbilical vein)
3/7	187
3/9	192
3/12	126
3/16	95

90 mg. and that in the umbilical artery 85 mg. The blood sugar of the baby during her unconsciousness was 38 mg.

The blood cholesterol of the mother on the day of confinement was 225 mg. per 100 cc. The blood cholesterol of the baby at the same time was 74 mg. and on the 3rd day of life 68 mg.

Discussion

The five cases described are remarkable from different points of view. The influence of pregnancy on the diabetes of the mother cannot be predicted with any certainty. In Case 1 the first pregnancy ended with diabetic coma, whereas in the course of the second pregnancy a remarkable improvement of the sugar tolerance was noted toward the end of the pregnancy. In Case 2 the patient showed considerable increase in the severity of the diabetes at the end of the pregnancy. Case 3 showed, without a marked increase of glycosuria, an alarming increase of the ketone bodies in the blood and urine with the end of the pregnancy. Although others have reported improvement of the sugar tolerance at the end of the pregnancy, I can record only one such case, namely, Case 1 in the second pregnancy. In the other pregnancies the contrary was noted. At about the end of pregnancy a diminished sugar tolerance appeared. Since it is known from the investigations of Carlson and Ginsburg[13] and Pack and Barber[14] that internal secretions of the pancreas can penetrate through the placenta, it might have been expected that the fetal pancreas would help support the metabolism of the mother. But evidence of such effect could only be supposed in the second pregnancy of Case 1. This aid was not sufficient to compensate for depression of the tolerance caused by the pregnancy itself.

In Cases 1 and 2 the mothers nursed their babies, one of them only for a short time. Aggravation of the diabetes by the lactation could not be observed. On the contrary, in Case 1 considerable improvement began during childbirth, as in some of Wilder's patients.[2]

The observations made on the carbohydrate metabolism of the babies are of particular interest.

The blood-sugar level showed a tendency to descend to hypoglycemic values several days after delivery. Amounts between 45 and 70 mg. per 100 cc. were repeatedly observed during a single day. Similar amounts were also noted by Randall and Rynearson.[22] Three babies had spells of unconsciousness several times during the first days of life. This was promptly relieved by glucose injection. In two cases a normal blood-sugar level was attained only five days after birth. Creveld[15] states that the fasting blood sugar of children of healthy mothers may decrease to extremely low values in the first month of life, and Schretter and Nevinny[16] have shown low levels during a fasting state in the first days. On the other hand, Rowley,[17] Morriss[18] and, recently, Helwig[19] have found the blood-sugar level of the babies of diabetic mothers to be not abnormally low. Creveld points out that in those cases in which he had found extremely low blood-sugar values no clinical evidence of hypoglycemia ever appeared. Therefore, it is remarkable that repeated unconsciousness has been observed in three cases among those described here. It is also noteworthy that the babies of diabetic mothers seem to differ from other children, since the tendency of the blood sugar to diminish to very low values was again noted a short time after an injection of glucose.

The low blood-sugar levels repeatedly noted may be explained by an overfunctioning of the pancreas of the children of diabetic mothers. The second of my patients gave birth to a living baby in her third pregnancy, but it died in a few days as a result of birth injury. I had the good fortune to obtain an examination of the pancreas of this child by Heiberg.[20] The gland weighed 5 gm., and the islets of Langerhans were well developed. Nakamura,[21] who inspected pancreases in different periods of life, found the weight of this organ to be 1.4 gm. in a baby who had lived only one day, and 1.5 gm. in a baby four days old. The gland of a baby of six days of age weighed 1.4 gm., of seven days 1.5 gm., and of eight days 1.8 gm. The weight of 5 gm. was not attained till the third to fifth month of life. The pancreas in Case 2 was therefore three times the size of the gland of the average newborn child. It is assumed that the hypoglycemic state of the children of diabetic mothers is due to the hypertrophy of the baby's pancreas. The fetus nourished by the blood of the mother has a permanent surplus of carbohydrate in the form of sugar that she is unable to burn. This excess leads to hypertrophy of the gland and to an increased production of insulin. The increased supply and utilization of the carbohydrates offered by the mother probably account for the frequently observed fact that the children of diabetic women are extremely big and excessively fat. In the milder cases of diabetes, the increased amount of insulin produced by the fetus seems to be sufficient to improve the condition of the maternal carbohydrate metabolism, and in the first days after birth leads to the hypoglycemic state of the baby, as described above.

Recently Helwig[19] has examined the pancreases of children of diabetic women and has found, in the vast majority, amounts of pancreatic tissue considerably larger than those in the children of nondiabetic mothers. Of 9 cases examined he apparently found in 3 a normal number of islets of Langerhans. He states that in the first case — that of a fetus in the sixth month — the gland weighed 0.8 gm. The pancreas in the second case — that of a fetus in the seventh month — weighed 1.2 gm., and the gland in the third case — that of a fetus of eight months — weighed 5 gm. Considering that, according to Nakamura,[21] the pancreas of a child born at full term weighs 1.2 gm., and that it attains a weight of 5 gm. only after the third to the fifth month of post-partum life, one must conclude that these three pancreases were abnormally heavy.

Since the hypoglycemia disappears after a few days, one may assume that the overproduction of insulin in the baby of the diabetic mother ceases, and that the islets of Langerhans in the pancreas become adjusted to the needs of the organism.

The cholesterol of the diabetic pregnant women was found to be increased, as is generally shown in the literature. Although some of the patients suffered from severe diabetes, the severity seemed to have no particular influence on the cholesterol values. I found in only one case a cholesterol level of over 300 mg. per 100 cc. Four of the 5 babies had cholesterol values between 58 and 74 mg. Joslin[10] also states that in newborn babies of diabetic mothers the cord blood cholesterol has ranged from 50 to 65 mg.

The cholesterol is highest in the maternal blood, lower in the umbilical vein and lowest in the umbilical artery. In only one baby was there a cholesterol level of 162 mg. per 100 cc. in the umbilical artery, which is extremely high in this period of life. In this case the cholesterol in the umbilical artery was higher than that in the umbilical vein. On the second day after birth this baby developed an icterus neonatorum that disappeared about the tenth day of life. On the third day, shortly after the beginning of the icterus, the cholesterol was 187 mg., on the eighth day it was 126 mg. and on the twelfth day, after the jaundice

had disappeared, 95 mg. per 100 cc. The mother had the highest cholesterol level among the pregnant diabetic patients. But it is unlikely that the high level of the child was inherited from the mother, because the cholesterol of the umbilical artery was higher than that in the umbilical vein and because the baby's cholesterol continued to increase in the first days of its life. Perhaps the high cholesterol should be considered the first sign of the jaundice that developed later.

The observations here described were made during the course of several years. The children developed well and continued to be healthy. The prophylactic cesarean sections were undertaken in patients who had had stillbirths, miscarriages or living children who died a few days after birth. They resulted in the birth of living, healthy children. Considering the extremely high mortality of children born of diabetic women allowed to go to the normal delivery, it is fair to assume that cesarean section as a prophylactic measure offers a more favorable prognosis. Among five children thus delivered no mortality was noted.

Summary

Five diabetic women with a past history of several abortions and stillbirths were successfully delivered by prophylactic cesarean section.

The high mortality rate of children of diabetic mothers may be decreased by this procedure.

The influence that pregnancy will have on the diabetes of the mother cannot be predicted in any case, in spite of careful treatment. In the same patient, pregnancy at different times may take a very different course.

A state of hypoglycemia in babies during the first days of life sometimes accompanied by periods of unconsciousness is described. The cause of this condition is the hypertrophy and overfunction of the pancreas.

The cholesterol level of the newborn babies ranged from 58 to 74 mg. per 100 cc. Only one baby had a value of cholesterol of 162 mg. This baby later developed an icterus neonatorum.

Considering the extremely high mortality rate of the fetuses and children of diabetic women, prophylactic cesarean section offers a favorable outlook. Therefore, this procedure is recommended to save the life of the endangered fetus.

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MEDICAL PROGRESS

THE PHYSIOLOGIC AND THERAPEUTIC EFFECTS OF HYPOTHERMIA*

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COOLING of the superficial layers of the skin has been employed as a physiotherapeutic procedure for countless centuries. Shivering accompanies the sensation of "coldness," and the subject may complain that he is "freezing." There is not, however, a significant lowering of the internal temperature of the body, and except in certain unusual circumstances, the depression rarely exceeds 2 or 3°F. This minor variation stands in sharp contrast to the heroic depression of body temperature (10 to 20°F.) employed recently in the treatment of certain pathologic conditions.

A general lowering of the body temperature was described in the lay press less than two years ago as another procedure useful in the treatment of patients with cancer, and the most optimistic reports alluded to it as "another cure" for cancer. The terms employed in describing the treatment included "freezing," "frozen sleep," "hibernation," "refrigeration" and "crymotherapy." An objection may be raised against the use of each of the terms. "Freezing" and "frozen sleep" are misnomers. No part of the body is frozen; in fact, during most of the treatment the body is exposed to temperatures considerably higher than 32°F., and the purpose of the procedure is to lower body temperature generally, meanwhile exercising great care to avoid freezing any tissue. Fay[1] prefers the term "hibernation" for a general lowering of the body temperature, and "refrigeration" for local cooling. Vaughn[2] has chosen "experimental hibernation," and Gerster[3] and Sauer,[4] "crymotherapy." Hibernation is a more acceptable term than freezing, but it is not ideal. Physiologic hibernation is peculiar to certain animals only and not to man. Furthermore, in the hibernating state of animal life the body temperature falls to within a few degrees of that of the environment. In the procedure under discussion, the temperature differential between body and environment is from 20 to 50°F. Crymotherapy could be rejected on two counts. If one wishes to anglicize Greek roots, the composition would be cryotherapy[5] rather than crymotherapy. Secondly, one's interest in the effect of low temperatures might well extend beyond its therapeutic possibilities. It is believed that the nomenclature would be more accurate if "hypothermia"[6] were selected to describe the procedure. It is a scientific term and is not medical jargon. It will be retained in this report wherever it is convenient to refer to a lowering of body temperature.

The initiation of interest of Fay and Henny[7] in low temperatures was associated presumably with the observation that primary and metastatic cancer rarely involve the parts of the body where reduced temperatures prevail,[8] that is, reduced as compared with the organs and portions of the body where optimal high temperatures prevail. Thus the extremities are rarely the site of neoplastic tissue and enjoy a low temperature in contrast to the breast, which has a high temperature and is involved frequently with cancer. In pursuing this subject, Smith and Fay[9] investigated the effect of temperature on the growth and development of the chick embryo. Exposure of eggs to temperatures that varied between 85 and 95°F. for from two to four days at the beginning of the incubation period — the remainder of the incubation proceeding at the optimal temperature (100.5 to 101.0°F.) — resulted in the retardation of growth and the appearance of regressive changes. Developmental malformations were equally prevalent.

In the first clinical report of these authors,[9] hypothermia was reported to be extremely useful in the treatment of cancer. After a relatively short period of trial, — approximately two years, — this statement has been rigidly qualified. Hypothermia is not recognized as a cure for cancer at present by even the most optimistic of its proponents. It does have a place, however, in the treatment of a selected group of patients suffering from this malady. Furthermore, a study of the physiologic changes associated with a lowering of body temperature may clarify certain problems concerning carbohydrate metabolism, conduction of the nerve impulse, mental processes, the cardiovascular system, the function of the kidneys and the heat regulatory mechanism. Lastly, hypothermia may find extensive application in the rapidly expanding

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field of general medical therapeutics. It seems opportune, therefore, to present this progress report.

The majority of the patients treated by hypothermia reported by Smith and Fay[9] were suffering from inoperable and frequently metastatic cancers. The internal temperature of the body was reduced about 10°F. by exposing the nude anesthetized patient to a bed of cracked ice. The ice was removed subsequently, and general hypothermia was maintained for twenty-four hours or longer by keeping the environmental temperature below 60°F. Certain impressive results were noted. In every case there was a prompt reduction in pain. In many patients the reduction became complete and persisted so for several weeks. This is of particular interest because many had required from 5 to 10 gr. of morphine daily for relief of pain, and several had been referred to a neurosurgical service for chordotomy. By the continued use of local cold for several weeks following the general hypothermia, it was possible to avoid surgical intervention, and in most patients to prevent the subsequent return to large doses of sedatives.

> Furthermore, there has been regularly a rapid, gross, measurable decrease in the size of the lesion within twenty-four to forty-eight hours. In a few cases, this has been as much as 50 per cent. This decrease in size had progressed steadily during the course of treatment. There has been a general improvement in the patient's condition, with a gain in weight, a better appetite and a change for the better in the mental state. There has regularly developed a notable tendency toward healing of previously intractable ulcerative cutaneous lesions and fistulous tracts. It must be remembered that these patients had all been given up from the standpoint of the more orthodox methods: operation and irradiation. There has been a marked retardation in recurrences, and the rate of growth during recurrences has been definitely diminished, as shown by careful studies by one of us (Smith) of several biopsy specimens taken at intervals during the course of treatment. In at least two instances there has been complete disappearance of the local lesion.[9]

This very encouraging report has been modified[1] recently without lessening the significance of the earlier contribution.

Before proceeding with the topic under consideration, it may be of interest to inquire about the lowest internal temperature that man can tolerate. Contrary to previous medical teachings, it probably lies somewhere between 70 and 75°F., and not between 90 and 95°F. In 1875 Reincke[10] reported the findings on five inebriated persons who had accidentally been exposed to cold. The rectal temperatures after admission to the hospital of the two who recovered were 75.2 and 86°F. respectively. The three who did not recover had temperatures of 79.5, 80.6 and 83.1°F. respectively. Nicolaysen[11] observed a rectal temperature of 76.4°F. in an acutely intoxicated patient, who recovered. During therapeutic reduction of body temperature, Fay[1] observed a minimum of 74°F. in one patient who did not survive treatment. Under similar circumstances Dr. Kenneth J. Tillotson and I[6] have observed a patient whose rectal temperature reached 74°F. at one time and whose temperature remained below 80 for more than ten hours. A second patient in our series had a recorded rectal temperature of 75°F. Recovery was uneventful in both. It is possible that these are above the critical level under ideal conditions, that is, in a hospital under close medical supervision, but they are probably not far above this level.

Homoiothermic animals (nonhibernating mammals), such as the cat,[12] the domestic rabbit[13] and the monkey (*Macacus rhesus*),[14] on the other hand, have been known to live following a reduction of body temperature to as low as 56 or 60°F. It is not certain whether this represents a real physiologic difference between lower animals and man, or whether it is related to the greater risk that may be taken with animals and the sacrifice of many to achieve an extremely low temperature in a few. The heat regulatory mechanism presumably ceases to operate below 75°F. in animals, and the continued fall in body temperature proceeds at the same rate as that in a dead animal under similar circumstances.[12] If the animal is then warmed, the thermal regulatory mechanism begins to assert itself at approximately 75°F. In the hibernating animal, the body temperature may approach 32°F. without causing death.

For additional information concerning hypothermia in human beings one must be satisfied with a very limited bibliography. There are several explanations for this. The employment of general hypothermia in the practice of medicine is recent. Only a few hospitals have been actively interested in the problem, and the number of workers in the field is small. The induction and maintenance of general hypothermia require considerable technical equipment and professional attention, and are not without danger to the subject. Because of the unavoidable risk associated with each treatment, it is probably desirable that only a few hospitals explore the therapeutic possibilities of hypothermia for the present. If a hazardous procedure such as this were mishandled, it might well fall into unwarranted disrepute before the facts and fallacies accompanying it were clearly defined.

Induction and Maintenance of General Hypothermia

The methods employed by the various investigators for the preparation of the patient and the

induction of hypothermia are similar. Written permission to conduct the treatment should be obtained from the patient or the legal guardian. A laxative may be administered the night before induction, followed in eight hours by an enema. It has seemed preferable to take patients who have not eaten for twelve hours, but probably this is not imperative. Three or more grains of Nembutal are given intramuscularly twenty minutes before the patient is placed in a cold environment. The sedative effect of Nembutal is desirable, but its most important action is on the heat regulatory mechanism. A drop in the body temperature is achieved without difficulty if the patient is prepared with Nembutal; otherwise, it may be very difficult, other aspects of the treatment being equal. When the stage is set, the patient is prepared finally with an anesthetic that is effective over a relatively short period of time. For this, from 0.5 to 0.7 gm. of Evipal, given intravenously, has been very satisfactory in my experience. As soon as the anesthesia has achieved its full effect, a rectal thermocouple* is inserted, and the patient is placed nude in an environment of approximately 32°F. Either especially constructed blankets† or cracked ice may be employed for the induction of hypothermia. Within an hour, the anesthetic effect of the Evipal has for the most part worn off, and simultaneously the body temperature decreases. The anesthetic property of the cold[13, 15] usually obviates the necessity for further intravenous anesthesia or sedative. All the patients whom Dr. Tillotson and I have studied have been relatively quiet without further anesthesia when the body temperature has been maintained below 90°F. During the induction of hypothermia, the temperature drop may be as rapid as 3°F. an hour, or as delayed as 0.5 an hour. When the desired minimal body temperature is approached, the environmental temperature is raised. Since an internal body temperature less than 80°F. approaches the critical level, we have endeavored to maintain a working range for internal temperature between 80 and 90°F. By alternately lowering and raising the external temperature, the internal temperature may be controlled within a range of 2 to 3°F.

In the earlier studies of Fay and Smith, the period of hypothermia did not exceed three days. The term of treatment was extended as the work progressed and as the body appeared able to tolerate longer sessions. If one wishes to refer to a "record," I have not found any reference that exceeded an eight-day treatment.[1] The body temperature was maintained at a level of approximately 85°F. the greater part of the time. It is the current belief that regressive changes in metastatic tissue associated with general body temperatures below 90°F. are not evident until a temperature as low as this has been maintained for a minimum of five days. In some patients intermittent periods totaling more than three hundred hours must be tried. The failure of Vaughn[2] to duplicate Fay's results may be attributed in part to the duration of treatment. Vaughn induced hypothermia in 6 patients, and maintained hypothermia for an average of not more than thirty-six hours. The treatments were not repeated. He stated that "the procedure was hazardous and not justifiable in the treatment of hopeless metastatic carcinoma." Fay has supervised approximately one hundred and seventy-five treatments since he began them in December, 1938, and believes that further study is indicated. I concur in this belief.

Fay[1] has deemed it advisable to go through a trial treatment of not more than twenty-four hours to gather information concerning the reaction of the patient to the procedure. Undoubtedly, this is important for patients who have metastatic cancer or who are older than forty. It is probably unnecessary for patients who are in reasonably satisfactory physical condition, and who are younger than forty. Following the initial treatment there may be one or more additional periods of from two to four days each. The intervals between successive treatments may be as short as two or three weeks. It is unknown just how many times the treatment may be repeated or whether many permanent harmful effects follow a large number of successive treatments.

The patients, usually, are drowsy and stuporous during the treatment, but they are not comatose unless they are sedated heavily or unless the body temperature goes below 80°F. Some observers allow the subjects to eat solid food from time to time. In an attempt to collect satisfactory metabolic data in our series, we have preferred to introduce measured amounts of water, salt and glucose by way of a stomach tube. Most patients have tolerated 50 cc. of 5 per cent glucose in normal saline by this route every thirty minutes. Gastric absorption of food and fluid appears to proceed at a normal rate in human beings exposed to cold.[16] In dogs,[17] the emptying time of the stomach decreases slightly.

When it has seemed desirable to terminate the treatment, which usually is an arbitrary decision, the external environmental temperature is allowed to approach 70°F. It has been our experience that a gradual restoration of body tem-

*A continuously recording instrument (Micromax) is manufactured by Leeds and Northrup, Philadelphia, Pennsylvania.

†Blankets adapted for a continuous flow of refrigerant are manufactured by the Therm-O-Rite Products Company, Buffalo, New York.

perature, that is, not greater than 2°F. an hour, is associated with fewer ominous signs than a rapid rise. Following restoration, most patients show a rise above normal for a short time.

Complications and Mortality

We have observed no serious post-treatment complications. Some of the patients have developed mild edema of the extremities for a few days. No other physical findings have been observed in those who before the treatment were relatively sound physically. Neither an upper respiratory infection, pneumonia nor acute nephritis has appeared in any of our patients. This is of interest when considered together with the observation of Foord[18] that the agglutinin production of rabbits increases following exposure to cold, the increase persisting for as long as twenty-four hours after exposure. Autopsy findings of patients dying from cancer have confirmed the impression that normal tissue is not harmed by general hypothermia.[19, 20] Furthermore, healing of tissue proceeds uninterruptedly during local hypothermia, with a minimum of scar formation.

Fatalities have occurred within twenty-four hours after treatment. In our series there were two deaths among twenty patients. Both were from cardiac failure, and both occurred during the period of hypothermia. One was probably preventable, the other was not. The first death occurred very early in the series, when the necessity for slowly warming the patient during restoration of body temperature was not appreciated. The second death occurred in a woman suffering from extensive metastases from a primary carcinoma of the breast, scirrhous carcinoma of the stomach, coronary heart disease and morphinism. She was a very poor risk, and hypothermia was considered only as a last resort. She died during treatment after her body temperature had been maintained between 86 and 89°F. for thirty hours. If one discounts this death, the mortality rate in our series is low. This statement is not made, however, to minimize the risk of treatment. The experience of other observers with chronically ill patients is similar to ours. Cardiovascular failure and pneumonia have accounted for most of the fatalities. The development of pneumonia in patients with metastatic cancer in the lungs is sufficiently common to cause rejection of such patients for treatment.[21]

Physiologic and Biochemical Phenomena Observed During Hypothermia

Changes in the vascular system develop early; they are profound in magnitude and marked in their variations from the normal. Following an initial rise of pulse and blood pressure, there is a gradual fall of both until the minimum body temperature is reached. In human beings the heart rate rarely falls below 50 a minute, whereas in nonhibernating animals exposed to cold, it may slow to 14 or 16.[13] The changes in pulse and blood pressure are associated with a marked vasoconstriction, arterial and venous, which becomes general as the temperature declines. Obliteration of peripheral venous channels, such as may be observed during casual exposure of an extremity to the cold, is noticed first. Drawing of venous blood becomes very difficult and may subsequently be impossible in a person who presents no difficulty at normal body temperature. With continued hypothermia, constriction of the large arteries occurs, and frequently one is able neither to elicit the radial or brachial pulse nor to obtain a blood-pressure reading in the customary manner. The blood pressure and peripheral pulse may be unobtainable for several hours, yet vascular occlusion or thrombosis is not a complication. Blood does flow in the arterial channels, however, because arterial punctures are possible, and in our series furnished most of the samples used for determining the concentration of the various blood constituents.

An increase in the circulation time of venous blood and a decrease in volume of circulating blood are other consequences of prolonged vasoconstriction. The circulation time from arm to leg may be prolonged two or three times over normal.[22] Observations of blood and plasma volume have not been reported for man, but in animals Harkins and his associates[23, 24] have observed a decrease in blood volume. This is the result presumably of the migration of fluid from the vascular channels into the interstitial spaces.

Cardiac arrhythmias, sinus arrhythmia and auricular fibrillation are frequently observed during treatment. The lower the body temperature, the greater the likelihood of the development of an arrhythmia.[25] All our patients whose temperatures reached 80°F. developed fibrillation. Digitalis, quinidine and restoration of body temperature are effective in correcting this disturbance. Electrocardiograms taken during hypothermia show fairly constant changes. In a series of 9 patients, Kossman[25] noted an alteration in the form of the final ventricular deflection and a prolongation of electrical systole. A high take-off of the T waves and a diphasic T_2 have also been reported. During recovery, the QT interval does not return to normal immediately; in fact, several days may elapse before this occurs. Tomaszewski[26] has re-

ported detailed observations on a man, aged fifty-four, who suffered from accidental exposure to the cold, but did not die until after he had been observed for several hours in the hospital. When he was seen first his heart rate was 21 per minute. Before death, the rate increased to 44. The electrocardiogram showed prolongation of the PR interval, low voltage and delayed conduction time. At autopsy, no significant morphologic changes in the heart were detected. In the dog, Otto[27] observed inversion of the T waves after chilling of the right ventricle with ethyl chloride, and a high take-off of the T waves after chilling of the left ventricle.

The formed elements of the blood undergo as diverse variations from normal as the cardiovascular system. If the fluid balance is not maintained, hemoconcentration follows with an increase in red-cell count as great as 25 per cent above normal.[28] The white-cell count increases several-fold with a rise in the percentage of polymorphonuclears. The percentage of reticulocytes also increases.[2] The sedimentation rate and the platelet count decrease. Within forty-eight hours after restoration of body temperature, the sedimentation rate returns to the pretreatment level.[29]

Scattered observations have been made on the chemical constituents of the blood. In view of the statement by Smith and Fay[9] that renal function ceases during hypothermia, it is of particular interest to inquire into the concentration of nonprotein nitrogen of the blood. Vaughn[2] observed a significant decrease in this constituent in 4 out of 6 patients during treatment. In 2 patients, there was an increase. Bernhard[29] observed an increase in 2 patients only, and no change in the remaining 24 of his series. The other constituents that have been studied — calcium, phosphorus, chloride and cholesterol — show no significant change during treatment.

Routine urine analyses for albumin, sugar and formed elements are negative.

Since the hibernating animal has a metabolic rate below normal it seems reasonable to expect that in human beings during general hypothermia a similar depression of this function might be detected. Patients with metastatic cancer who are given therapeutic amounts of sedatives periodically during the treatment show such a depression.[30] If the cold alone is relied on for sedation, it is possible that the rate may be unchanged or above normal. A final decision in this matter must await further investigation. Obviously, it is desirable to learn how important an altered oxygen consumption is in the production of the therapeutic and physiologic effects described.

Pupillary reflexes disappear in human beings during hypothermia[31] as they do in animals[14]; crossed tibial reflexes and the absence of plantar response have been observed. The loss of nerve conduction appears to be a direct effect of cooling.[32] During recovery a restoration of the abnormal responses occurs.

Hypothermia offers an interesting opportunity for the study of shivering. All patients shiver shortly after exposure to the cold environment unless they are heavily sedated. Fay[1] observed a disappearance of shivering when the temperature fell below 90°F. This has not been our experience with patients who have been given no drugs after the induction anesthesia. We have observed patients to shiver intermittently as the temperature fell to as low as 75°F., just as animals shiver at low temperatures.[33, 34] On the return toward normal temperature, shivering is less violent. There are two explanations for the individual variation in shivering. I am inclined to attribute cessation of shivering in Fay's series to the periodic use of sedatives. Hypoglycemia is another antishivering agent. In the dog, insulin may abolish shivering due to cold.[35] It is possible that some patients develop spontaneous hypoglycemia during hypothermia, and shivering is subsequently inhibited.

Burton and Bronk[36] noted two types of muscle tremors in the anesthetized cat following cooling. When the rectal temperature fell below 93°F., intermittent and inco-ordinated twitches of single units appeared. A rise of oxygen consumption followed shortly. The response appeared first in the muscles of the head and thorax, then in the superficial pelvic muscles, and lastly in the deep muscles of the extremities. The response of a given muscle increased in regularity by the number of active units, and in frequency from 5 to 12 per second. Later, co-ordinated grouping of discharges appeared and resulted in gross tremors, and shivering (11 per second). A single unit discharged only once in each group. That a similar phenomenon occurs in human beings was mentioned as a possibility by Denny-Brown and his associates.[37] Undoubtedly, further study of hypothermia will clarify this matter.

Therapeutic Considerations

General hypothermia has been used for the treatment of several conditions. These include intractable pain, cancer, morphine addiction, leukemia and schizophrenia. The treatment was devised originally for patients suffering from cancer. Although definite regressive changes in undifferentiated cell growth in deep metastatic lesions have not been observed consistently, hypothermia has

a place in the treatment of selected patients suffering from neoplasias. Relief of pain may well be the most important therapeutic gain, and all observers who have reported on the subject are in agreement concerning this effect. So successful has it been that Fay[1] no longer considers narcotics necessary in the treatment of intractable pain and "operative intervention for pain [chordotomy and rhizotomy] has not been required during the past two years."

Approximately two thirds of the patients who complain of pain and who submit to hypothermia experience reasonably prolonged periods of relative or complete freedom. There are several cases in which patients who required several grains of morphine daily for control of pain before treatment became quite free from pain, without opiates, following hypothermia. Systematic relief appears to be independent of the location of the tumor. Pain secondary to new growths of the brain, antrum, buccal cavity, thyroid gland, breast, lung, stomach, sigmoid, rectum, kidney, adrenal gland, testis, prostate, bladder, cervix, vulva or skin has responded. The duration of relief varies. Some patients are helped for only a few days; others may remain symptom free for as long as four months. The effect of cold on pain is noteworthy and clinically important.[38] Precisely why the anesthetic effect on the sensory nerves should persist for several months is not understood.

Not only does pain associated with tumors respond, but simultaneously, regressive changes in neoplastic tissue have been evident on microscopic examination. The response of sarcoma is less striking than that of carcinoma. The more undifferentiated the carcinoma, the more rapid is the regressive phenomenon. Primary tumors as well as lymph nodes that have been invaded have undergone diminution in size. In certain patients with tumors of the gastrointestinal tract, the regressive changes have been so extensive that the tumor has sloughed out of the wall of the involved region, with the development, later, of peritonitis.

It is advisable to inquire whether general hypothermia increases the rate of growth of tumor tissue or damages normal tissue. No evidence has been accumulated to suggest that the rate of growth of tumor tissue is accelerated. So long as the temperature is reduced, any effect on growth is retardative. Similarly, it has been shown that significant cell changes in normal tissues are most infrequent.

Probably more important than general hypothermia in the treatment of cancer is the use of local hypothermia. The application of cold locally in the treatment of tumors was discussed by Cooke as early as 1865[39] as follows:

> Cold, by means of ice applied with great caution, has its uses. It subsides those occasional inflammatory paroxysms to which scirrhous tumor is prone, and may check the disposition to suppuration, the result of inflammatory action. Its constant use, however, in all states of the tumor is not warranted by experience. The destructive power of this agent is so great, that I have seen the whole breast slough as a result of the prolonged application of ice, and the sloughing, in the instance I refer to, extended through the intercostal muscles into the cavity of the chest.

Recent studies have shown that regressive changes are most obvious when local hypothermia can be carried out at a temperature between 40 and 50°F.[21] Special fitting coils through which a refrigerant circulates are applied. As observed by Cooke, necrosis of tumor tissue may follow. Rarely, there may be complete disappearance of tumor cells as observed histologically in successive biopsies. It has been observed in some patients who succumbed to the cancer and who came to autopsy that the treated primary site was quite free of tumor cells.

McCravey[40] has reported favorable results with local hypothermia in 5 cases of carcinoma of the bladder. By marsupializing and exteriorizing the bladder cavity, especially designed metal applicators were enabled to enclose partially the lesion and bladder cavity. In each patient on whom this was carried out, the local bladder tumors were reduced in size or destroyed, all or in greater part, within from six to twelve weeks. The deeper extension of such tumors when it had not been possible to maintain accurately the desired temperature showed regressive changes, but some tumor tissue persisted. In all cases the patient's life was prolonged beyond that expected for a patient not treated with hypothermia.

The phenomenon of regression has been summarized by Smith and Fay.[19]

> Granular hydropic and fatty degenerative changes may be observed in the cytoplasm of the cells, depending largely on their individual character and origin. In many instances the ratio of nucleus to cytoplasm is so distorted that little evidence of cytoplasmic change can be observed. The cytoplasmic changes are followed by or associated with nuclear degeneration. More frequently pyknotic condensation of the nucleus occurs, ending in actual rupture of the nuclear membrane. It has been our experience, as has already been indicated, that the more undifferentiated such tumor cells are, especially if they belong to the epithelial series, the more rapid and extensive are the regressive phenomena. Histologically, the effects of this physical agent, cold, are not so unlike the effects of that physical agent which has been more carefully studied in respect to cell changes, roentgen radiation.

It is possible that radiation combined with cold[41] might be a more effective agent than either one alone, just as cold renders plant cells more sensitive to radiation.

It is difficult to reconcile these observations of the effect of cold with other experimental observations in the literature, particularly those that concern the behavior of animal tumors. Lambert[42] showed that cancer cells are more resistant to cold than cells of the normal adult. Auler and his associates[43] exposed the Flexner carcinoma and the Jensen sarcoma of the rat to temperatures as low as 32°F. The tumors were then transplanted. Most of the transplants grew. It was assumed that the tumors formed sporelike cells that were resistant to the cold. Tumor transplants maintained at a temperature from 70 to 98°F. were more successful than those maintained at 98°F. Bischoff and his associates[44] studied sarcoma No. 180 in 29 mice. The body temperature of the animals was reduced as low as 65°F. No permanent effect on the growth process was noted.

Several patients suffering from leukemia have been treated by hypothermia. Reich[28] has reported 2 such cases. One patient was in the terminal stages of aleukemic lymphoblastic leukemia. No changes attributable to the treatment were observed. The second patient was suffering from acute myeloblastic leukemia. The total white-cell count decreased from 50,000 to a normal level during each treatment, and remained within the normal range for several days. No change in the differential count — 95 per cent myeloblasts — was observed. The diminution in the white-cell count of patients with leukemia is quite the reverse of the process observed in patients who present no disturbance of white-cell economy.[2] That further investigation of the use of hypothermia in leukemia is indicated seems obvious.

Closely associated with the relief of pain is the treatment of morphine addiction. Patients with cancer who have required large amounts of opiates for relief of pain before general hypothermia have been able to live afterward without such drugs for several months. In others, smaller doses of sedatives than formerly have been required to control symptoms. Similarly, morphine addiction per se has responded to general hypothermia. Most patients require only one period of a few days for a favorable therapeutic effect.

The use of cold in diminishing the undesirable effects of intoxication has been appreciated for some time. This is evident from a description reported in 1803.[45]

> A Gentleman of this Island, whose name was Weeks, a great votary of Bacchus, was in the practice, from fifteen to twenty years, of plunging into cold water when he rose from his bottle, and of actually going to sleep in a trough full of water, with his head supported on a kind of wooden pillow made for the purpose, above the surface. When he dined abroad, and had not the convenience of his own trough, he used to strip off his coat, waistcoat, and shirt, and sit exposed in the open air, and in that situation go to sleep, whether it rained or not. And sometimes he went and bathed in the nearest adjoining pond, to which he generally required assistance to be conveyed. The effect of this practice was, that instead of experiencing debility, lassitude, headache, and nausea, he found himself on awakening cheerful and refreshed, and free from all the effects of intoxication. In the year 1789, dining one day abroad, he got alternately drunk and sober three times before midnight, each time recovering his sobriety by himself by immersing himself, and sleeping in cold water; and on awakening returning to the company. The last time, after supper, he was so immoderately intoxicated, that he insisted on his companions undressing him and conveying him themselves to the pond. They carried him accordingly in a chair, and set him up to the chin in water, where he continued upwards of an hour, a person supporting him. I heard this last circumstance from a gentleman, one of the party, whose veracity may be entirely depended on.
>
> At home, however, he used, as I have already mentioned, a trough made for the purpose, with a bench in it as a pillow, having been nearly drowned when sleeping in his pond, from the negroe who was appointed to watch him, having himself fallen asleep. In this watery bed he would sleep, one, two, three, or even more hours, experiencing always the greatest refreshment. His wife and family, when they wished him to change his quarters, used to draw out the plug, and let the water run off, when he awoke and humorously complained of the loss of his bed-clothes. At length this expedient began to lose its effect in rousing him and one time, he continued to sleep in an empty trough. In consequence of this, he was seized with extreme rigors and chills, followed by a severe attack of rheumatism, which affected him a long time, and made him desist from the practice in the future. But to the end of his life he was in the habit of sitting, when intoxicated, with his clothes open, and sometimes quite naked, exposed to the wind and the rain. This extraordinary character died of apoplexy about three weeks ago, aged sixty-three.

In recent months Dr. Tillotson and I have studied the effects of hypothermia on patients suffering from schizophrenia.[6] Ten patients were studied, 4 of whom were subjected to two or more periods of general hypothermia. Most of the patients had been treated previously with insulin or Metrazol, or both, without benefit. All those who were older than thirty years and who had been confined to a mental hospital for a long time showed little or no prolonged alteration in their mental symptoms. On the other hand, of those who had been sick for less than three years all except one showed a reassuring alteration in their clinical courses. In 4 patients the improvement has been striking and continuous for six months. In 3, marked temporary improvement was noted.

It is appreciated that the total number of patients is small, but with promising results, continued efforts are justified.

Other Conditions To Be Investigated

The conditions discussed above may serve little else than to introduce the subject of therapeusis by hypothermia. The field of possibilities for the future may be large. The reader, undoubtedly, has visioned benefit in such disturbances as Hodgkin's disease, lymphogranuloma venereum, subacute bacterial endocarditis, parasitic diseases, undulant fever, chronic arthritis, acquired syphilis, acute toxic psychoses, tetanus, multiple sclerosis, intractable migraine and encephalitis.

Summary

Observations on the experimental reduction of the internal temperature of the body as well as local application of cold constitute the basis of this report. A discussion of hypothermia is timely because the physiologic changes and therapeutic implications associated with it have begun to be studied systematically only of late. During general hypothermia the internal body temperature may be lowered to 75°F. with subsequent recovery. It may be maintained continuously between 80 and 90°F. for as long as eight days. If local application of cold is employed, a circumscribed area of the body may be maintained between 40 and 50°F. for several months without damage or destruction of normal tissue.

Relief of pain is probably the most important single effect of general hypothermia in patients with metastatic cancer. Regressive changes in tumor tissue have been reported following prolonged general hypothermia, but are observed more constantly following prolonged local hypothermia. Other conditions that have appeared to benefit from general hypothermia include morphine addiction, leukemia and schizophrenia.

It should be appreciated that knowledge in the field of hypothermia is most fragmentary and that until a large amount of painstaking labor is expended, a full and comprehensive understanding of all the related facts will not exist.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27071

PRESENTATION OF CASE

A sixty-three-year-old unmarried woman entered the hospital complaining of abdominal pain and jaundice.

Since the patient was drowsy and not co-operative, the history was obtained largely from her relatives. It appeared that from early womanhood she had suffered from "bilious attacks" characterized by indigestion, nausea and vomiting. In more recent years the attacks had become more numerous and were accompanied by upper abdominal pain, which the patient was unable to localize accurately. These episodes were not accompanied by jaundice, chills or fever. Two weeks before admission she suffered a severe attack of upper abdominal pain accompanied by persistent nausea and vomiting, two chills and fever. She noticed that her stools were light in color and her urine dark, and one week after the onset of abdominal pain, marked jaundice appeared, with severe pruritus. At the time of admission the jaundice was subsiding, but the nausea persisted. Her appetite had always been good until the onset of her present illness.

It was stated that the patient had had jaundice once as a child and rheumatic fever at twenty-five with "a little heart damage," but no recurrence. When the patient was fourteen, her mother died of what was said to be "consumption."

On examination the patient was a well-developed, obese woman whose skin was dry, scaly and markedly jaundiced. The pupils were small and regular, and reacted to light and accommodation; the scleras were jaundiced. The skin of the abdomen, flanks and upper thighs was excoriated, and contained a number of slightly raised, reddish papules. There was a diffuse reddening of the nasopharynx, with a mucopurulent exudate. Examination of the heart was negative; the blood pressure was 135 systolic, 68 diastolic. There was slight dullness to percussion, with many fine rales on auscultation at both lung bases. The abdomen was obese and pendulous, and a tender, vague mass was palpated in the right upper quadrant, extending medially into the epigastrium. Rectal examination was negative.

The temperature was normal, the pulse 90, and the respirations 30.

Examination of the urine showed a + test for albumin and a + bile reaction, with 20 white blood cells per high-power field.

Examination of the blood showed a red-cell count of 4,200,000 with a hemoglobin of 11.9 gm. (photoelectric-cell technic), and a white-cell count of 61,000 with 98 per cent polymorphonuclears. A van den Bergh showed 40 mg. of bilirubin per 100 cc. of serum, biphasic. The prothrombin time was 31 seconds (normal, 16 seconds), and the hematocrit reading 39.4 per 100 cc. The nonprotein nitrogen of the blood serum was 130 mg. per 100 cc., the serum protein 5.6 gm. per 100 cc., and the blood chlorides 96.6 milliequiv. per liter.

X-ray films of the abdomen, taken with a portable machine, were not entirely satisfactory because of the patient's size, but no definite abnormalities were noted. The right side of the diaphragm was probably elevated.

The patient was given intravenous fluids and one 500-cc. blood transfusion. On the third hospital day the white-cell count had fallen to 41,800, and the nonprotein nitrogen to 100 mg. per 100 cc., but the prothrombin time had risen to 43 seconds. Seven days after admission the temperature was 100°F. and the following day had risen to 102. On the ninth hospital day the patient was operated on. A 15-cm. incision was made in the right upper quadrant of the abdomen. Numerous fresh adhesions were encountered, and there was a sudden gush of thick, greenish-black bile from what was presumably an old, friable, gangrenous gall bladder. Everything was gently palpated, and no stones could be felt. Further exploration was deemed inadvisable, and one rubber tube was sewn into the gall bladder and a cigarette wick placed beside it. The wound was closed carefully, using silk for the fascia.

Postoperatively the patient's condition remained precarious, the temperature averaging 100.2°F.; the wound drained small amounts, never more than 15 cc. of bile-stained fluid. She was given daily intravenous injections of 1500 cc. of 75 per cent glucose in physiologic saline solution and many blood transfusions. Five days postoperatively she had a chill and complained of a sharp substernal pain. On examination her color was ashen, and she responded poorly. The temperature was 104°F., the pulse 122, weak and irregular; the blood pressure was 96 systolic, 60 diastolic. Respirations were 27, and were groaning and shallow. There was bronchial breathing with dullness at the left base, and bilateral basal rales. The patient was placed in an oxygen tent, but death

occurred the following day. Latterly the nonprotein nitrogen rose to 110 mg. per 100 cc., and the serum van den Bergh dropped to 6.4 mg. of bilirubin per 100 cc.

Differential Diagnosis

Dr. Leland S. McKittrick: May we see the x-ray films?

Dr. Richard Schatzki: The portable films are very unsatisfactory, as the record states. There is a little more to be seen on the films than stated in the record. There are areas of atelectasis in both lower lung fields. One cannot see the spleen. There are no visible gallstones, but gallstones would have to be fairly large to show in a film of this quality.

Dr. McKittrick: Thank you. The films do not confuse me more than the written report, and that is always a help.

Here is the story of a sixty-three-year-old woman the early part of whose history I cannot make much out of and have to disregard. I do not know what is meant by "bilious attacks." As I listen to patients complaining of "biliousness," they are just as apt to use this term for episodes of migraine as for gall-bladder attacks. In more recent years the attacks became more frequent. There were no chills, jaundice or fever, but the patient did have abdominal pain at about that time, and it is possible that the bilious attacks were attacks of pain. Otherwise she was perfectly well until two weeks before admission to the hospital, and we are therefore dealing with an acute process, consisting of a sudden severe attack of upper abdominal pain accompanied by persistent nausea and vomiting, two chills and fever. The stools became light in color and the urine dark, and one week after the onset of abdominal pain, marked jaundice with pruritus appeared. If one takes the recorded facts, — progressively frequent attacks of indigestion, some with pain, culminating in a sudden severe attack of pain, chills, fever, light-colored stools, dark urine and jaundice, — then I think one might rightfully assume that the patient had gallstones, that one or more stones had dropped into the common duct, and that she had in addition a cholangitis.

On physical examination she was found to be very obese, to be severely jaundiced, to have excoriations secondary to the itching that goes with jaundice, and to have a big mass, palpable in the right upper quadrant, which extended medially into the epigastrium. The temperature was normal, and the white-cell count was 61,000 with a little secondary anemia. Presumably there was no blood dyscrasia because 98 per cent of the white cells were polymorphonuclears. She had a very high bilirubin: 40 mg. There was a rapid prothrombin time, an elevated nonprotein nitrogen, a slightly lowered serum protein, and a normal blood chloride. The picture at this point becomes confusing, because she became drowsy and the nonprotein nitrogen rapidly climbed to 130 mg. per 100 cc. Despite the normal temperature, the white-cell count remained notably high. The urine showed a + test for albumin. I am impressed with the rapid prothrombin time only two weeks after the onset of an apparently acute process. It seems to me that such a patient must have something more than can be explained on the basis of a common-duct stone, with or without an acute gall-bladder condition. I am inclined to believe that the drowsiness, the high nonprotein nitrogen and the early development of a rapid prothrombin time are evidences that, in addition, she must have had a good deal of liver damage due to acute hepatitis or perhaps hepatic insufficiency.

I shall assume that she had gallstones, but that that is not the whole story. A number of other conditions must be considered, but there is not time to discuss all of them in detail. The disproportion between the temperature and white-cell count in a patient who is so sick so soon after the onset of symptoms makes one think of acute pancreatitis in association with a common-duct stone. However, the evidence is so much in favor of hepatic insufficiency and the findings are so definitely right-sided that I should prefer some other explanation. A pylephlebitis is, I presume, a definite possibility, but I should not be able to make this diagnosis. I should operate on the assumption that she had gallstones. I believe that she had a stone in the common duct and cholangitis, and for the reasons already described, severe intrahepatic disease. To explain the mass in the right upper quadrant I should have assumed a large, distended gall bladder, but in view of the additional information obtained at operation there must have been a perforation, and this probably represented an abscess in relation to the gall bladder and adjacent structures. Even though no stones were found at operation, I assume that they were present.

I do not see how one can be certain why the patient died so suddenly. She had a rapid prothrombin time, but she had a lot of transfusions, and one would have thought that the transfusions would have controlled any bleeding tendency. She might have had a pulmonary embolus. I do not think that was the cause of her death. Progression of the biliary-tract disease might well have been enough.

I should hate to give the impression that I have any confidence at all in my interpretation of these findings. I simply believe that the patient had gallstones, in addition to something more to explain this picture, and I should like to put all the emphasis on the liver. Whether or not she had pancreatitis I do not know, but I doubt it.

DR. HORATIO ROGERS: If you account for the mass on the basis of abscess, you still leave the discrepancy between the temperature and white-cell count not accounted for.

DR. MCKITTRICK: Yes; I have not been able to account for it entirely. Of course this patient was not absolutely afebrile; the temperature was slow to climb, but did start up at the end of a week in the hospital.

DR. RICHARD WARREN: Dr. Richard H. Miller operated on this patient but could not be present today. We went through the same course of reasoning as Dr. McKittrick, but without arriving at such a concrete decision. She was sent in with a diagnosis of stone in the common duct, and for the first day or so, we assumed that that was what she had. The more we thought the story over,—the normal temperature, the elevated white-cell count and the fact that she had bile in the stools,—the more the whole preoperative picture confused us. The mass, which was not palpable when she first arrived, appeared during the nine days preceding operation. The question was whether to operate and when. I might say, in justification of the operation, that the prothrombin time had dropped to 20 seconds by the day of operation and the nonprotein nitrogen to 60 mg., so that she was not quite so sick as the data in the abstract indicates. At operation the mass that we came down upon was assumed at first to be the gall bladder, but it was not in the gallbladder fissure, because the falciform ligament was definitely coming out in that area. Since the patient was in such poor condition, and since bile drained freely from this cavity, a tube was inserted in it for drainage, and nothing further done.

CLINICAL DIAGNOSES

Acute pancreatitis.
Auricular fibrillation.

DR. MCKITTRICK'S DIAGNOSES

Cholelithiasis, with acute cholecystitis and pericystic abscess.
Choledocholithiasis.
Cholangitis.
Acute hepatitis, with hepatic failure.

ANATOMICAL DIAGNOSES

Choledocholithiasis.
Acute cholangitis.
Multiple abscesses of the liver.
Pulmonary edema.
Icterus.
Operative wound: drainage of liver abscess.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: At autopsy it was still impossible to identify the gall bladder. There was a large abscess in and beneath the liver in the region of the falciform ligament, and the drain had been placed in this abscess. There was a stone in the common duct that completely obstructed it. Above the stone the biliary system was markedly dilated; below, the duct was narrow, and in fact there appeared to be a definite stricture extending from the stone down 2.5 cm. to the ampulla. The liver was enlarged, and on section was found to contain many abscesses filled with deeply green-stained purulent material. Many of these abscesses could be traced to definite contiguity with the dilated biliary radicles. Cultures showed hemolytic streptococci. This extensive intrahepatic cholangitis was probably the chief cause of death. There was a story of rheumatic heart disease in childhood, and although the mitral valve itself seemed negative, we found some calcification of the annulus fibrosus of the ring—a somewhat unusual lesion, though not an extremely rare one.

The lungs showed atelectasis and extensive edema, but almost no pneumonia.

A PHYSICIAN: What about the kidneys?

DR. MALLORY: The autopsy was done rather long post mortem and showed something that we frequently see in heavily jaundiced patients, occasionally in some other conditions: a sort of lysis of connective tissue throughout the body. The liver cells in such cases fall into jumbled masses, owing to disappearance of the reticulum. The same thing was apparent in the kidneys and the voluntary muscles. The sections are worthless to look at. One cannot possibly say whether or not she had nephritis.

CASE 27072

PRESENTATION OF CASE

A fifty-five-year-old housewife entered the hospital complaining of vaginal bleeding.

The patient's menstrual periods had always been regular until six years before admission, when they increased to twice a month and she noticed the occurrence of frequent hot flashes.

After a year their character changed to small hemorrhages of bright-red blood lasting a week or longer, with staining for four or five days thereafter. Three years before entry the patient suffered a profuse hemorrhage, which lasted a week. She was admitted to another hospital, where an unstated operation was performed, which included, however, an appendectomy, right herniorrhaphy and hemorrhoidectomy. After this procedure, occasional gushes occurred, with staining for four or five days once a month. One year before admission the vaginal bleeding again became profuse, and during the last two months before entry, staining was noticed every day. The hot flashes had disappeared, but she complained of easy fatigability and exertional dyspnea, with occasional dizzy spells when walking. The patient had had two children and one miscarriage.

She had had the usual childhood diseases. The family history was noncontributory.

On examination the patient was very obese and did not appear ill. Examination of the heart and lungs was negative; the blood pressure was 160 systolic, 80 diastolic. Examination of the abdomen showed old surgical scars in the midline and in the right lower quadrant. On palpation it was difficult to feel the uterus, but a large mass believed to be the uterus could be felt bimanually and per rectum. The cervix was slightly eroded, but otherwise negative.

The temperature, pulse and respirations were normal.

Examination of the urine showed a ++ test for albumin, with 40 white blood cells per high-power field, and many bacteria. Examination of the blood showed a red-cell count of 4,100,000. A blood Hinton test was negative.

An operation was performed on the second hospital day.

Differential Diagnosis

Dr. Marshall K. Bartlett: Of course, we should like to know what was found in the abdomen three years before admission, when the previous operation was performed. I think we must assume that if any significant lesion had been found in the pelvic organs and any of them had been removed, we should have been informed about it.

In a woman of fifty-five with vaginal bleeding the first decision to be made is whether the bleeding is due to cancer. There is nothing in the record on which I can make that decision. We can be reasonably certain that the bleeding was not from a malignant lesion in the cervix on the basis of the pelvic examination. Did she have carcinoma of the endometrium? I do not believe it would give a tumor that would be described, as this is, as a large mass. As you all know, the uterus becomes somewhat enlarged, but it would not be described as a large tumor, unless there was extension into the surrounding structure. Then a large mass might be present, but I think that would be recognized by fixation and so forth. Is this a tumor of the ovary, or is it a fibroid tumor of the uterus? I do not see that we can tell. It is frequently impossible to decide, even when one can examine the patient personally, and I can only accept their statement that it was thought to be uterus, although I see no way of ruling out ovarian tumor. I shall assume that the tumor was in the uterus. In that case the most likely thing would be a fibroid or multiple fibroids, which could account for the bleeding, but it would not necessarily rule out carcinoma of the endometrium in addition. In a considerable number of cases, endometrial carcinoma is found in uteri that contain fibroids. The best conclusion I can come to is that the patient had fibroids of the uterus; there is the possibility that she had carcinoma of the endometrium in addition.

Dr. Tracy B. Mallory: What would your procedure be?

Dr. Bartlett: A diagnostic curettage, a frozen section and a laparotomy should be performed.

Dr. Mallory: Are there any other suggestions?

Dr. Joe V. Meigs: What do the hot flashes mean?

Dr. Bartlett: I suppose she had begun to have the menopause.

Dr. Meigs: They came and went. It makes one think of some ovarian dysfunction.

Dr. Bartlett: Yes.

Dr. Meigs: The intermittent hot flashes bring up the question of an endocrine disturbance such as a physiologic cyst. In a person who has any sort of functional cyst or tumor of the ovary you may see just such a thing. When the estrin is high enough, the patients lose their flashes, and when it is not, they have them. It is a possibility.

Dr. Bartlett: It is a possibility; I had not thought of it. If that were so the endometrium would give a picture to confirm the diagnosis.

Dr. Meigs: At fifty-five she might have a granulosal-cell tumor, with active endometrium but probably no hot flashes. The hot flashes disappear with the development of this particular tumor.

Dr. Benjamin Castleman: How about the staining every day? What does that mean?

Dr. Meigs: It might mean a polyp in the endometrium. She might have had either carcinoma or functional bleeding.

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Clinical Diagnosis

Adenocarcinoma of the uterus.

Dr. Bartlett's Diagnoses

Fibroids of the uterus.
Endometrial carcinoma?

Anatomical Diagnosis

Polypoid adenocarcinoma of the uterus, Grade I.

Pathological Discussion

Dr. Mallory: A curettage was done on this patient and very abundant material obtained that looked grossly very much like carcinoma. The frozen section was not particularly helpful; the material was composed of such well-differentiated glands that it was difficult to decide whether it was a polypoid carcinoma or simply an atypical polyp. The outstanding feature, however, was the fact that there was no stroma,—each gland backed up against the next gland without any intervening stroma,—and on that ground a diagnosis of cancer was considered justified. A hysterectomy was done. The ovaries, as well as the tubes, were small and atrophic on both sides. The uterus was considerably enlarged—about twice the normal size, I should say. The entire fundus was filled with a papillary tumor that showed very slight invasion of the myometrium. How long the tumor may have been present, there is no way of guessing.

Dr. Meigs: Do you think that a polypoid type of hyperplasia does become malignant? Novak* states that there is often hyperplasia with adenocarcinoma.

Dr. Castleman: We have had two or three cases with hyperplasia and carcinoma in different parts of the same uterus, and this would fit in with Novak's idea.

Dr. Mallory: I cannot remember a case showing simple hyperplasia on curettage that came back two or three years later with carcinoma.

Dr. Meigs: This particular case suggests that there might have been such a development starting six years before.

Dr. Franklin G. Balch, Jr.: What are your ideas at the present time, knowing that this was carcinoma, in regard to immediate surgery versus x-ray treatment?

Dr. Meigs: If you have a perfect radium setup, use it, and then operate. By a perfect setup I mean the proper way to apply it; we have it nowhere around Boston except at the Pondville Hospital.

*Novak, E. and Yui, E.: Relation of endometrial hyperplasia to adenocarcinoma of the uterus. *Am. J. Obst. & Gynec.* 32:674-698, 1936.

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INFLUENZA

During the great pandemic of 1918–1919, the number of deaths from influenza throughout the entire world was greater than the total number of persons killed in the five years of World War I. It is not surprising, therefore, that, because of the many similar situations existing today, physicians and laymen alike are following with a great deal of interest reports of increases in the incidence of influenza in various parts of this country. They are all greatly concerned with the possibility that the reported outbreaks represent the preliminary phases of another pandemic.

Just what has been learned during and since the last pandemic that may be of help in preventing or controlling the ravages of another that may be forthcoming? Briefly, much information was acquired during the 1918–1919 pandemic concerning the clinical, pathological and epidemiologic features of the disease, and a great amount of data was accumulated, which, though not conclusive, has shed considerable light on its etiology. The results of many studies made during the last few years have clarified the etiologic aspects still further. New tools have become available for the study of influenza and similar diseases, and the prospects for better prevention and control are considerably brighter today than they were a decade ago.

The first of the important recent contributions emanated from the Rockefeller Institute at Princeton and concerned swine influenza, the so-called "hog flu" of the veterinarians. Shope[1] showed quite conclusively that this disease is caused by a combination of a filterable virus and a visible bacterium, the latter having the biologic characteristics of *Haemophilus influenzae,* that is, the influenza bacillus of Pfeiffer, but differing from it in immunologic reactions and pathogenicity. In hogs, the filterable agent, that is, the swine influenza virus alone, produces only a relatively mild upper respiratory infection similar in most respects to uncomplicated human influenza; the visible organism, *H. influenzae suis,* by itself produces no demonstrable disease; but the combination of the virus and the bacillus produces a severe type of influenza, with a pneumonia similar to that observed in man during the great pandemic and with a correspondingly high fatality. The similarity of Shope's findings with what is known of the bacteriology and epidemiology of human pandemic influenza, added to the fact that the disease in swine was first recognized during the 1918–1919 epidemic and has recurred almost annually since then, lends support to his theory that the swine disease took its origin from man at that time. These findings also suggest that the severe and highly fatal form of human influenza may be of complex etiology and may involve both filterable viruses and visible agents. In man, the earlier experiences suggested that more than one visible agent may be involved and that, although the Pfeiffer bacillus may play a role in many cases

and in some epidemics, streptococci, staphylococci and pneumococci play the important secondary role in others.

With respect to the disease in man, a great advance was made when Smith, Andrewes and Laidlaw[2] succeeded in transmitting an infection to ferrets from typical cases of epidemic influenza. This was accomplished by intranasal instillation of filtrates from throat washings. The disease in the ferret differs from that of swine in that visible bacteria take no part in the infection. The hog virus, however, exhibits the same characteristics in the ferret. The filterable virus discovered by these workers, or viruses having the same pathogenicity and similar immunologic characteristics, have now been isolated from many epidemics in this country and in widely scattered places throughout the world. Numerous workers have already added considerably to our knowledge of the biology of the virus and the epidemiology of the infection with which it is associated. The virus can now be transmitted to mice, and it can be grown in tissue cultures and in the tissues of the developing chick embryo. The earlier studies with the influenza virus have suggested that separate serologic races of influenza virus may exist, and this has been borne out by more recent studies. These types of strains from human cases have been labeled "influenza A virus," "influenza B virus" and so forth, and the infections from which they are obtained are called influenza A, influenza B and so forth, respectively.

Animals infected experimentally with these viruses, and persons having clinical influenza during epidemics in which such viruses were recovered develop neutralizing and protective antibodies in their blood, or have an increase in titer of preexisting antibodies. The experimental animals also develop resistance to reinfection. The duration of the immunity is relatively short, lasting from a few weeks to several months. The antiviral antibodies do not develop or increase in persons who have other respiratory infections, such as common colds, bronchitis and pneumonia.

A number of vaccination experiments have been made in animals, and some of the results have been of sufficient interest to warrant a limited trial under carefully controlled conditions in human beings. Such investigations are now being conducted purely as experiments, but the results are being awaited with considerable interest. There are no satisfactory data concerning therapeutic experiments with immune serums produced by inoculation of animals with virus, and animal studies with such serums have not been too encouraging. Convalescent serums from human cases were used during the 1918–1919 epidemic in the treatment of a limited number of cases, with variable and mostly equivocal results. It is possible that the use of larger doses given earlier in the disease may prove more efficacious. The sulfonamides are entirely without effect on the virus. It is to be expected, however, that these drugs may favorably affect the secondary pulmonary infections when hemolytic streptococci, pneumococci or staphylococci are involved. There is also the possibility that the pathogenic bacteria cultured from cases of typical influenzal pneumonia are of only minor significance. This is suggested by the fact that in the ferret and in the mouse, the chief pathologic features may be reproduced by virus alone provided that the dose and virulence are adequate. In that event, chemotherapy would have little to offer. The effects on *H. influenzae* cannot be reliably predicted from available data, but will probably not be extraordinary.

Most physicians who had extensive experience with influenza during the 1918–1919 pandemic will probably say that the disease as seen then was radically different from that which has occurred in sporadic outbreaks during the last few years and which they are now seeing. Any deductions based on studies carried out recently must, therefore, be made with the reservation that the pandemic disease may be different in many respects from that occurring during smaller and milder epidemics that are included under the same clinical diagnosis of influenza.

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NATIONAL CANCER RESEARCH

THE grants-in-aid, totaling $271,277.50, that the National Advisory Council has awarded to various institutions and persons constitute a significant contribution to the eradication of cancer; this council was set up by congressional action to advise the Surgeon General of the United States Public Health Service on all matters concerning the federal government's program for cancer research, and the funds, the distribution of which it supervises, are made available by congressional appropriation.

Grants amounting to $129,085 for fundamental cancer research went to Harvard University; the University of Cincinnati; the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine; Duke University; the University of Chicago; Dr. B. R. Nebel, of the Experimental Station of New York; Institute of Cancer Research, Columbia University; Dr. John J. Bittner; Cornell University; the Barnard Free Skin and Cancer Hospital, St. Louis; the Michael Reese Hospital, Chicago; the Memorial Hospital, New York City; and Louisiana State University.

An additional $92,570 was granted to the University of California, the University of Michigan and Washington University of St. Louis for experimental work on the cyclotron, the so-called "atom-smashing" machine, which produces radioactive particles that may prove to be valuable in treating cancer.

The National Research Council (for the American Registry of Pathology), the American College of Surgeons, the New York Hospital, the University of California, Meharry Medical College, of Nashville, Tennessee, and Dr. Harrison S. Martland received a total of $49,652 for clinical cancer research.

The projected studies of radioactive substances to be produced by the cyclotron now being built by the Carnegie Institution, of Washington, D. C., represent further progress in cancer research; these experiments will be carried out through the collaboration of the Carnegie Institution and the National Cancer Institute. The latter has a staff of thirty-eight scientists, fifty technicians carefully trained for specific investigations and a laboratory that is the largest of its kind in the world and is also complete with modern equipment.

The help that the Government is extending for research and treatment represents a praiseworthy contribution to the fight against cancer; the experiments stimulated by the grants-in-aid are a step in the direction of control and possibly eventual eradication of the disease.

OBITUARY

ERNEST AMORY CODMAN

1869 – 1940

Ernest Amory Codman, surgeon, good Bostonian and crusader, was born on December 30, 1869, and died on November 23, 1940, the victim of a painful, prolonged disease following many years of poor health, which he had borne with fortitude. A crusader is one who makes a difficult, dangerous campaign to save something precious, and without thought of gain for himself. Amory Codman's crusade was to ensure for all in need of surgery what he believed to be ideal treatment. Being an independent thinker of vigorous mind, whose emotions were easily stirred, he employed unconventional methods to accomplish his purpose. Perhaps he inherited this tendency from his militant grandfather, the Reverend John Codman. When this Congregational minister became aware that his flock was likely to be contaminated by the teachings of his brother preachers, he refused to allow any other than his own discourses in his church in Dorchester. A hostile element placed another minister in the pulpit and protected him there by a guard. But John Codman climbed up the steps as high as he could, addressed the congregation and walked out with a large majority of those in the church. The opposition soon gave in.

One would not have expected, perhaps, so striking a professional career from this particular Codman's beginnings. He attended a well-known boarding school, enjoyed the usual sports and made good friends among a variety of individuals. An excellent scholar, he ranked high in both school and college. Very early in his boyhood he took to hunting and fishing, sports which he pursued vigorously all his life, for which he always kept himself prepared, and which enabled him, in fact, to withdraw from and forget at intervals his excit-

ing professional life. Few have made better use of an avocation.

As a house pupil at the Massachusetts General Hospital in 1894–1895, he began to do original things. He kept the first ether charts with the idea of showing how harmless a good anesthesia could be. During his years in the Harvard Medical School, he had visited Vienna, where he learned of the importance of disease of the subdeltoid bursa and so secured his introduction to the shoulder joint. This became the love of his professional life, from which he was sometimes diverted but to which he always returned, the subject, finally, of his remarkable book.

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When the roentgen ray was discovered in 1895, Codman was one of the first to explore its possibilities, and with his characteristic thoroughness he secured from physicists at Harvard and Technology the best advice and assistance available. It is even more characteristic that, having made complete roentgenologic studies of the important joints of the body, at considerable expense in time and money, all without being asked to do so by anyone, he should have presented his collection to the Warren Museum, where it was buried. Many years later, he came upon his atlas, dusty and apparently forgotten, an event which strengthened the conviction which earlier experiences had created, namely, that his labors were not likely to be recognized. As will presently appear, this attitude of mind, a sense of isolation, a feeling that others would not readily agree with his views, was a strong influence in his life, a peculiarity which in its most violent form caused him to introduce his astonishing cartoon dealing with hospital efficiency and in its mildest form led him to remark to one of his companions in partridge hunting that his dogs were always, like himself, a little queer. It is typical of his own appreciation of this quality that at one moment he should have consulted two alienist friends to inquire whether or not, in his battle for hospital efficiency, he seemed to them the victim of a dominant idea. But his self-consciousness about this matter was never morbid; he was not so introspective as all that. Indeed, he was often more than a little amused at himself.

The turning point in Codman's career came when he was about forty. He had gone up the ladder at the Massachusetts General Hospital and had become an assistant visiting surgeon, associated particularly with Dr. F. B. Harrington. He had begun to write timely, original papers, calling attention, first, to perforated duodenal ulcer and then to its chronic obstructing form. At about this period also, having put the subacromial bursa on the map, his interest in bones and joints, the fruit of his work in the roentgenologic field, had caused him, with Dr. Henry M. Chase, to write an authoritative paper dealing with the hitherto unexplored subject of injuries to the bones of the wrist, under the title, "Fracture of the Carpal Scaphoid and Dislocation of the Semilunar Bone." He had also repaired with success the ruptured supraspinatus tendon. He was making a good living along rather conventional lines. At this time his conviction "that every hospital should follow *every* patient it treats long enough to determine whether or not the treatment has been successful, and then to inquire, If not, why not?" became the great interest of his life. The products and by-products of his efforts to convince others of the value of this scientific and entirely reasonable idea were truly extraordinary. They included a share in the creation of the American College of Surgeons, and especially its widely accepted standardization of hospitals. They included the Registry of Bone Sarcoma, the enthusiastic services of his hospital staff in the Halifax disaster, the remarkable meeting of the Suffolk District Medical Society and, finally, his book on the shoulder.

A visit to England in 1910 by the Society of Clinical Surgery seems to have been the occasion of the actual creation of the American College of Surgeons. Very likely the idea had been in the minds of many, but Codman tells how he and Dr. Edward Martin, of Philadelphia, discussed the end-result idea in a hansom cab, how hospitals might thereby be improved and how Martin held that "the tail is more important than the dog, but we shall have to have a dog to wag the tail." In 1912, when Martin was made president of the first formal Clinical Congress of Surgeons of North America (the initial step in the creation of the American College of Surgeons) he appointed Codman chairman of the Committee on Hospital Standardization, out of which came in the following year Codman's address to a great gathering on "The Product of a Hospital," in which he preached the revolutionary doctrine that institutions were responsible for the work of their staffs. He called on hospitals to study the product of each surgeon, analyze his results, compare them with those of others and actually enable the public to choose the appropriate surgeon for each disease.

Several years earlier, his desire to demonstrate how a hospital should be conducted had caused Codman to establish one of his own. He took the opportunity, offered by the publication of a series of annual reports, to discuss his success

or failure in each patient treated, explaining the bad results as due to errors of skill, judgment, care and so on. It must be supposed that this excessive frankness and his insistence on an assay by each hospital of the contributions of its staff helped to create, locally, in the profession an atmosphere rather hostile or at least resistant to his ideas. His resignation from the Massachusetts General Hospital in protest against promotion by seniority rather than merit did nothing to dispel this atmosphere, and when he asked to be reappointed and made surgeon-in-chief, on the ground that a study of his results over a ten-year period showed them to be better than those of others, he gave an impression of egotism which hurt his cause. Actually, this seeming boastfulness arose from his desire to be entirely consistent, or if you like, from his "New England" conscience. The record, he held, should govern. His own was open to inspection. Moreover, he believed that in a position of authority he could best carry on the end-result system.

The climax of his campaign was the meeting at the Boston Medical Library. As chairman of the surgical section of the Suffolk District Medical Society, he had arranged a comprehensive discussion of hospital efficiency. His difficulty in securing the speakers on whom he had at first counted may have caused him to spring his surprise poster on the gathering. Perhaps he had had it in mind all along. In any event, he was a good enough showman to use the mayor of Boston as one of his speakers and to assemble a large and interested audience. Finally he presented his cartoon and explained its meaning. For the benefit of those not familiar with the episode, it should be explained that the cartoon, drawn by his friend, the artist, Philip L. Hale, centers about an ostrich. The bird represents the public. Its head is buried in the sand. It is laying golden eggs, which it kicks into the hands of the faculty of the Harvard Medical School and the staff of the Massachusetts General Hospital. Observations and queries are put into many mouths, and among the figures are several whose faces were true to life. Naturally there was a storm of protest, and Codman was, as he afterward said, in disgrace.

In the very revealing preface of his book on the shoulder, — he calls the book a balloon, of which the preface and epilogue are the basket, — he admits that he may have chosen his path badly, that he should have been either a leader or a satirist, not both. However, being at the same time a realist with a good backbone, he never regretted his escapade. Much of his purpose was accomplished. Special assignments of surgical subjects had already been given to particular men at the Massachusetts General Hospital, and more specialization followed. An end-result system was created not only at that hospital but over the whole country, an epoch-making achievement: all patients must be followed, for years if necessary; everyone must explain his bad results. The matter was carried far, though not so far as Codman wished. There was no formal ranking of the hospital staff, an impossible feature, as he should have known. Yet one can discern in many institutions a process of sorting out without publicity or formality. There has been a tendency to push particular surgeons into certain fields and to bar them from others. For his too-impulsive action at the library meeting Codman had to pay in loss of dignity, prestige and professional income — a small price, he believed, considering the great result.

Then came the war, the generous volunteering of his hospital staff — with end-result cards to test its efficiency — in the Halifax explosion (1917) and in the following year his unselfish military experience. Serving in this country, he had little opportunity to practice surgery, but found ample scope for his do-or-die spirit in fighting the tragic epidemics which had broken out. As always, he brought along, and made excellent use of, his end-result cards and, of course, his shotgun and fishing tackle.

He returned to civil life in debt, to find his hospital closed and himself somewhat disillusioned about his capacity to alter human nature. He tells that, after having patched up so many splendid young men, he had lost much of his enthusiasm for keeping the aged and infirm alive, and was so filled with a desire to make a little money that he gave up his hospital, which had always been a drain on him, and charged his patients much more than before. Yet when he failed to save one of them — the wife of an intimate friend — he became inspired to make his great fight against bone sarcoma, for which he received no earthly reward.

The Registry of Bone Sarcoma, started in 1920, and his book on the shoulder, published in 1934, though seemingly unrelated to each other and to his end-result idea, were equally a part of it. To begin with, he labored, through the *Boston Medical and Surgical Journal,* as it was then called, to find out if any physicians in Massachusetts knew of any cases of bone sarcoma, particularly of any cured cases. When he discovered, or seemed to discover, that no one read his appeal in the *Journal* or would take the trouble, if they had really done so, to respond, he sent out return

postal cards by the carton. On the subject of the shoulder and especially the disabling rupture of the supraspinatus tendon, which he correctly advertised to be an injury of great economic importance, he was even more disturbed that he could not secure recognition of his views or impose on the profession the need of prompt and successful diagnostic methods. Finally, he decided to write the best book on the subject, dedicating it to the end-result idea, through the American College of Surgeons. The main portion of the book, the balloon, is of course a masterful monograph on the shoulder; the preface and epilogue, the basket, as has already been told, are an arresting and revealing story of his character and life.

To understand Codman one must read the beginning and end of his book. If one thinks of him as in any sense a disappointed man, one will soon find that such was by no means true. He agrees that he has had a good time in life. He calls himself quixotic, but he intensely dislikes being dubbed a "reformer." He certainly describes himself as, though he does not use the word, a "crusader." His creed was to think of the future, to work for coming generations. If he seemed at times to violate good taste or even professional ethics, he did so with the idea of attacking sham and smugness, the horrors of his life. He never said hard things of those who disagreed with him, only of those whose motives he felt to be unworthy. And even then, he never attacked individuals. If he liked, he could hold his tongue. He may, in the outbursts of his crusading spirit, have seemed to be a child, but if so, he was an *enfant terrible,* never cried and never asked for another chance.

As a surgeon, Codman did not hold himself to be especially skillful, though he knew himself to be ingenious and resourceful. He was cut out to be, what indeed he was, a "forlorn-hope artist." He would see the possibility, which others might have overlooked, of succeeding in a desperate operation. In overcoming obstacles to this end, he might irritate and annoy a hospital staff, but at last he would accomplish his purpose and secure the approbation of everyone concerned. It was impossible to resist his fundamental goodness and charm.

Amory Codman had many devoted friends in many walks of life. No one could associate with him intimately without coming under the spell of his enthusiasm, his squareness and the attractive whimsical streak which, in all but his most strenuous moments, took the sharp edge off his intensity. In everyday life he was affectionate, thoughtful, fair, a good companion. His was a strong character, remarkably free from pretense and affectation, uncompromising, of a sort much needed in this day. He should be counted one of New England's great figures, a man who has left a deep mark and has deserved well of posterity, for whom he labored.

J. H.

MEDICAL EPONYM

Gordon's Sign

Alfred Gordon (b. 1869), of Philadelphia, instructor in nervous and mental diseases, Jefferson Medical College, wrote of "A New Reflex: Paradoxic flexor reflex; Its Diagnostic Value" in *American Medicine* (8:971, 1904).

> It has been my good fortune to observe a new reflex which I found present in cases, the history of which points to organic diseases of the nervous system, and especially of its motor tracts; I found it always associated with exaggerated knee-jerks; in some cases the Babinski reflex was present, in some not. . . .
>
> The reflex can be elicited in the following manner:
>
> The patient may either lie on his back or sit on a chair with the feet (not the legs) on a stool. The feet must be slightly rotated externally; in this position complete relaxation of the muscles of the leg is obtained. The examiner must always place himself to the outer side of the leg; the thenar and hypothenar muscles of his right hand must be placed on the inner surface of the tibia of the patient and the fingers press deeply upon the middle or the lower portion of the calf muscles. I say deeply because the pressure must be transmitted to the flexor muscles of the deep layer; sometimes pressure must be combined with lateral movements of the superficial muscles. If the reflex is present, extension of the great toe, or of all the toes, will be noticed. There is evidently no other .nuscle except the flexors that could be brought into display. . . .
>
> If excitation of the flexors produces an extension of the toes, the reflex is certainly paradoxic. . . .

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Pregnancy Complicated by Mitral Stenosis and Pneumonia, and Resulting in Cesarean Section

Mrs. F. W., a twenty-five-year-old primipara, was first seen on September 3, 1913, when she was approximately seven weeks pregnant.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

The family history was unimportant. The patient stated that she had had rheumatic fever and St. Vitus's dance as a child. There was no history of any other illness. Catamenia began at twelve, were regular with a twenty-eight-day cycle and lasted five days. The last period began on July 12, making the expected date of confinement April 19, 1914.

Physical examination revealed a well-developed and well-nourished woman. The lungs were clear and resonant; there were no rales. The heart showed no enlargement. There was a question of presystolic thrill, and a murmur that was double at the apex. The apex beat was forcible. The pulse rate was 80. The abdomen was normal. Vaginal examination revealed the uterus anterior and slightly enlarged.

The pregnancy progressed satisfactorily until February 27, when the patient reported that a cold, which she had had for several days, had become much worse. She was unable to breathe and had a bad cough. She also stated that she was having abdominal cramps. She was thirty-two weeks pregnant at that time.

On February 28, the temperature was 100°F., the pulse 110 to 120, the respirations 35, and the systolic blood pressure 95. She was seen in consultation, and a diagnosis of pneumonia at the left base was made.

On March 1 the patient's condition was improved. The temperature was 99°F., the pulse 92, and the respirations 25.

The patient grew steadily better, and when seen on March 24, was completely recovered. The blood pressure at that time was 100 systolic, and the pulse was 80. The lungs were clear and resonant; there were no rales. Examination of the heart was as before. There was slight edema of the ankles. The uterus was enlarged to a size consistent with her dates. The vertex was presenting, but was not engaged. The question of cesarean section arose.

The patient was seen weekly from March 24 until she started in labor on April 19. After a consultation because the head was still not engaged, cesarean section was deemed advisable, and the patient was delivered of a female child weighing 7½ pounds, the only complicating factor being that she lost more than the normal amount of blood. The convalescence was uneventful.

Comment. This case of mitral stenosis resulted from an attack of rheumatic fever and St. Vitus's dance. Today such cases should be seen at the beginning of the pregnancy by competent cardiologists to determine whether the pregnancy should continue, and to supervise the patient properly from the standpoint of the heart condition throughout the pregnancy. A cesarean section was done because the head was not engaged, and because most cases of mitral stenosis at that time were delivered in this way irrespective of the engagement or nonengagement of the presenting part.

The fact that this patient went through an attack of pneumonia when she was about seven months pregnant without signs of cardiac failure shows that the heart disease was well compensated. In spite of this it would have been much better if she had been confined to bed during the last six to eight weeks.

Subsequently, the patient again became pregnant and was aborted.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning February 16:

MIDDLESEX EAST

Tuesday, February 18, at 4:15 p.m., at the Melrose Hospital, Melrose. Obstetric Infections: Diagnosis and treatment. Instructor: A. Gordon Gauld. Walter H. Flanders, *Chairman*.

MIDDLESEX SOUTH

Tuesday, February 18, at 4:00 p.m., at the Cambridge Hospital, Mt. Auburn Street, Cambridge. Acute Abdominal Pain: Its interpretation and management. Instructor: Richard B. Cattell. Dudley Merrill, *Chairman*.

NORFOLK

Thursday, February 20, at 8:30 p.m., at the Norwood Hospital, Norwood. Chemotherapy in the Treatment of Gonococcal Infection. Instructor: P. N. Papas. Hugo B. C. Riemer, *Chairman*.

NORFOLK SOUTH

Monday, February 17, at 8:30 p.m., at the Quincy City Hospital, Quincy. Nutritional Deficiencies and the Uses of Preparations of Vitamins. Instructor: Harold J. Jeghers. David L. Belding, *Chairman*.

SUFFOLK

Thursday, February 20, at 4:30 p.m., in John Ware Hall, Boston Medical Library. Diagnosis, Treatment and Prognosis of Central-Nervous-System Syphilis. Instructor: Francis M. Thurmon. Reginald Fitz, *Chairman*.

DEATHS

RICHARDSON — ANNA G. RICHARDSON, M.D., of Roslindale, died February 1. She was in her eighty-first year.

Born in Lowell in 1861, she received her degree from the Woman's Medical College of Pennsylvania in 1891 and joined the staff of the Vincent Memorial Hospital a year later. She served successively as assistant surgeon, head surgeon and chief-of-staff until her retirement in

1929. For twenty years she was medical adviser to the New England Telephone and Telegraph Company.

Dr. Richardson was a member of the Massachusetts Medical Society and the American Medical Association, and was a fellow of the American College of Surgeons.

Two nephews survive her.

SANBORN — Perley L. Sanborn, M.D., of Marblehead, died February 3. He was in his ninety-first year.

Born in West Unity, New Hampshire, he attended Dartmouth College and received his degree from the Bellevue Hospital Medical College in 1877. He was a member of the staff of the Mary Alley Hospital in Marblehead, and was a member of the Massachusetts Medical Society and the American Medical Association.

A son and a granddaughter survive him.

CORRESPONDENCE

THE NATIONAL LEPROSARIUM AT CARVILLE, LOUISIANA

To the Editor: This note was written by a former associate of mine who is now teaching at Louisiana State University School of Medicine. I have greatly enjoyed reading it and think it will be of interest to the readers of the *Journal*.

Elliott C. Cutler.

Peter Bent Brigham Hospital,
Boston.

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Some time ago I visited the National Leprosarium at Carville, Louisiana, and found it very interesting. The Leprosarium is a Marine Hospital operated by the United States Public Health Service. Dr. McCreery, the officer of the day, took me on his rounds and talked very interestingly about leprosy, the hospital and many sidelights.

The State of Louisiana originally established the leprosarium in 1894, and it continued as a state institution until 1920, when the United States Public Health Service took it over. Prior to 1920, the United States Public Health Service appointed a board under the chairmanship of Dr. George W. McCoy to select a site for a national leprosarium. Because of the loss of sensation and heat regulatory function of the skin, patients with leprosy fare better in a subtropical climate, and the board therefore considered sites in Florida, California and Texas, the states other than Louisiana from which most of the cases come. However, each time a location was decided on, the surgeon general was informed of local opposition to the establishment of a leper colony, and another site had to be chosen. The problem was finally solved by taking over the state leprosarium by congressional action.

The leprosarium is located on the east bank of the Mississippi River, about sixty-five miles above New Orleans. The attending physicians, who are members of the United States Public Health Service, are assisted by several consultants in special fields who come up from New Orleans. Nuns are in charge of the nursing service, because it has been found to be impossible to hire lay people who will give satisfactory care to the lepers. The orderlies and helpers are patients whose leprosy is arrested or has regressed. They receive wages from the federal government for their services. Many of these orderlies are free to leave the hospital because of their improvement, but often they have no desire to go.

There are no wards, all the patients having private rooms. The original buildings consisted of a group of cottages, but a few years ago a large fireproof central building was constructed. It has a capacity of 65 patients and is called the Infirmary. All patients who require bed rest because of some systemic reaction or who have ulcerations on both feet are cared for here. A few rooms at the end of one corridor were equipped with heavy metal screen doors that could be locked. This provision has been made for mental patients with leprosy, but no patients of this type were in the hospital at the time of my visit.

All buildings are connected by wide "pikes" covered overhead and screened on the sides. These passageways are very wide, and beds, wheel chairs and bicycles pass through them without difficulty. At present about 50 patients ride bicycles from one building to another. This form of transportation is a great boon to many patients with one "bad" (ulcerated) foot, who would otherwise be confined to the Infirmary.

This collection of buildings — the cottages and the Infirmary — is distinct from the other buildings that house the medical staff and their families, and the employees of the institution who do not take care of the patients. But there is very little contact between any part of the colony and the outside. River boats pump oil into tanks just inside the levee, and with this source of fuel, the institution maintains its own heating, refrigeration, power and lighting plants, and is quite independent.

Most of the patients at the colony are from southern climes. Halfbreed Mexicans seem to be more susceptible to the disease than members of the white race. Many other patients are of Spanish or French origin. Some are Chinese, Japanese, Jewish, Italian, and, of course, colored. It is impossible to discern nationality after the disease has advanced to certain stages. Dr. McCreery told us about an exhibit of pictures of advanced cases of leprosy in patients of different nationalities. Although racial characteristics were easily noted in the early pictures, they were largely erased in the later ones.

The population of lepers in the entire colony during the last seven years has varied between 365 and 385 patients. About 60 cases are admitted annually, but these are not all new ones, since that figure includes some who have deserted instead of going through the routine of being released and readmitted and therefore may be counted as new patients. The 886 patients admitted up to 1938 came from Louisiana (212), Texas (148), California (168), Florida (65), New York (107) and other states (186). However, of the 349 inmates as of June 10, 1938, 140 were born outside of continental United States. Furthermore, many patients were born in states other than those from which they were admitted. Thus leprosy is a disease of aliens in California, but is a disease of native Americans in Louisiana. It has been estimated that the number of unsegregated cases, known and unknown to local health authorities, equals the number of segregated cases. Since Carville has the only leprosarium in the United States, it is readily seen that leprosy is not a numerically important disease in this country. However, an incidence of 50 cases per 1000 inhabitants has been reported in Africa.

Fewer deaths occur from leprosy than from rabies, the latter claiming about 50 lives annually in the United States. At Carville there are about 12 deaths annually, many of these being due to intercurrent infection. Approximately the same number become arrested cases. Some of the patients desert, but those who remain are cared for until something happens to change their status.

The morale of the leper is poor for the first week or ten days at the colony. There appears to be no euphoria as in tuberculosis. He soon makes friends with his kind, however, and many patients become quite cheerful. They have various indoor games to keep them occupied, and

the radio is a big factor in their entertainment. On the southern part of the grounds is a golf course for the use of those patients who are able to take advantage of it. They are dissuaded from being out in the heat of the day, since the bright, warm sun has a tendency to cause some of the lesions to flare up, and also because the patients tolerate heat poorly.

The privacy of the patients is constantly considered. Those seated in their rooms with their backs to the doors were not disturbed. We passed many rooms, presumably because Dr. McCreery knew that our entrance would be resented. Clinics are held weekly, but no patient is forced to attend them. They are asked once to go, and if they express a desire to be excused from attendance, they are not molested or asked again.

There are three varieties of leprosy, the nodular, the nerve and the mixed. The physical examination is important in the early diagnosis of the disease. Alteration in the degree of pigmentation, loss of hair from the eyebrows and, rarely, from the scalp, and atrophy of the skin are noted. Palpation will often reveal the rubbery induration so characteristic of the nodular form of the disease, and in the nerve type the peripheral nerves may be enlarged in a cylindrical, spindle-shaped or beaded fashion. Anesthesia and analgesia can be detected by the usual methods of testing cutaneous sensitivity.

Photographs are used quite extensively to record the findings. I saw some that showed very clearly the early loss of hair from the brows, and the parchment appearance of the atrophic skin. Other photographs recorded cases of ulnar, peroneal and facial nerve involvement. Another group of pictures represented x-ray studies of the bone lesions. The changes in the bones consist of simple absorption and are seen clearly in the small bones of the hands and feet. When pyogenic infection is superimposed on simple absorption, extensive bone destruction is seen. The portal of entry in these cases is usually an abrasion or laceration sustained inadvertently when the patients, who have lost their sense of pain, bump or scrape their hands or feet or burn themselves. To avoid burns from cigarettes, and to accommodate the flexion contracture of the phalanges of the hand, many lepers use very long cigarette holders.

In the laboratory the bacteriologist showed me some slides of the organism and called my attention to the characteristic palisade arrangement of the bacilli. They are found in large numbers in smears and biopsies in contrast to tubercle bacilli. Scrapings of the lesions yield a high percentage of positive smears, but sections are also taken. Nasal secretions are said to be the commonest source of material to be examined to demonstrate an arrested case, but the positive nasal scrapings are so constantly associated with demonstrable nasal lesions that any suggestion of the latter makes examination of the nasal secretions unnecessary.

The first patient we saw had been an advanced case when he was admitted to the colony many years before. Now all he has is some falling in of the nasal bones, slight atrophy of the skin, and evidences of recent operations on the face. I was shown a picture of this patient taken when he had arrived at Carville several years previously, and it was obvious that the lesions had improved markedly. His was the nodular type that causes the leonine appearance because the rubbery induration does not cross the natural skin folds or lines of cleavage. This patient had taken up hunting, and although he made great claims for his prowess in that sport, I was told that his sight was so poor, because of an iridocyclitis and associated corneal opacities due to ulceration, that he often made a mistake in identifying his game and its location. Some time ago he aimed his gun at what he thought was fair game but the charge went in the direction of a house outside the hospital grounds. The neighbor retaliated by sending a charge of buckshot at the patient, and some of it lodged in the skin of his face. The last of these had been removed just recently.

The youngest patient on record at Carville was three years old, but the disease has been seen elsewhere in a patient nineteen months old. The disease is very rare before the age of ten, yet children are more susceptible than adults. This seems to be a paradox, but the explanation lies in the long period of incubation. One patient was only nine years old and had been admitted to the leprosarium five years before, soon after the diagnosis had been made. His mother, who was also a leper, was admitted at the same time, but she died several months ago. Recently an aunt of the boy was admitted with very early lesions. This is an example of the familial predisposition to the disease that is seen in many cases. Although the boy is only nine years old at present, he has rather extensive lesions on his face and much swelling of his hands and fingers. This swelling, which may also involve the feet, seems to be a common accompaniment of the lesions and is without a general cause, such as renal damage or cardiac decompensation. I noticed that many of the patients had made openings in their shoes to make room for swollen feet.

A group of four patients in one room were listening to a radio program. I thought that one of them was quite young, but I was told that when the lesions become so advanced it is impossible to estimate accurately the age of a patient. The one in question was about thirty years old.

One patient had rather advanced leprosy, and as often happens in such cases, was beginning to show signs of kidney damage. He had edema of the abdominal wall and scrotum and considerable ascites. He had been given twelve doses of Salyrgan without any improvement. Although these patients show evidence of renal failure, no lesion characteristic of leprosy occurs in the kidney. However, nodular infiltration is found in the liver, making it appear to have been sprinkled with white pepper. This patient wore a tracheotomy tube because of laryngeal involvement. I learned that leprosy attacks the upper air passages, particularly the nose and larynx, but does not involve the lower respiratory tract. In the larynx, nodules form on the vocal cords, and scar-tissue contraction follows the ulceration that occurs. The resulting stenosis may cause slight changes in the voice early in the course of the laryngeal lesion, but later, obstruction occurs and acute changes in the obstructed area often necessitate emergency tracheotomy. On the other hand, the ulceration in the larynx may, by its destruction of tissue, bring about improvement by decreasing the degree of stenosis. This improvement, however, is temporary. The incidence of laryngeal involvement is much greater in leprosy than it is in tuberculosis. Three patients with tracheotomy tubes were seen on ward rounds. At one time fourteen patients were thus equipped, and the laryngeal involvement seemed to be almost epidemic.

Another patient had a septicemia due to the leprosy bacillus, and during this blood-stream invasion, fresh crops of macules came out at irregular intervals and were accompanied by exacerbation of constitutional symptoms. Blood cultures had not been done because of the persistent failure of attempts to cultivate the organism. This patient had a lesion on the radial side of the extensor surface of the left wrist. It was light red, brightest at the edge, and smooth and shining, showing a definite outline. Later the macules and the neighboring normal skin be-

came anesthetic. The center of the macule may become white and atrophic. The color of the lesions varies according to the natural pigmentation of the skin. In deeply pigmented skins the macules may be violaceous or copper colored. The reaction to the blood Wassermann test is positive in many cases of leprosy, and this finding, associated with skin lesions, has often prompted the diagnosis of syphilis. It is not surprising, therefore, that many cases of leprosy have been found in venereal clinics.

In guarding against contagion, simple cleanliness is all that is ordinarily practiced by the physicians, who wear gowns like those used in ordinary contagious wards. After examining patients and palpating some of the lesions with bare hands, thorough washing of the hands is considered sufficient precaution against the disease. I was told that during the last fifty years at this institution no case of leprosy had been considered attributable to contact between patient and personnel.

The organisms are found in biopsies of lesions of the anesthetic type if taken during the inflammatory stage. It is said, however, that this type of lesion is not responsible for spread of the disease because the organisms are not discharged from them.

Even when the disease is active, patients may be released for sufficient reason but must travel in a private conveyance. Often a patient whose wife may be ill or dying does not wait for an official release. He simply deserts, hops a freight train, and when the urgent matter is taken care of, he reports back to the institution. These patients encounter no difficulty in being readmitted.

Patients may be paroled when the lesions are considered inactive. Two factors are considered in arriving at this conclusion. The lesions must be inactive from every clinical standpoint, and examination of scrapings from the lesions must show no organisms on twelve different occasions. Such patients return from time to time for reexamination, and if the lesions become active again, they must return to the colony.

The only treatment other than excellent general hygiene consists of chaulmoogra oil. A supply of it is kept on the dining tables and is used at each meal. An ethyl ester of chaulmoogra oil has been used intramuscularly, and sodium chaulmoograte has also been given a trial. There is some doubt about the efficacy of these preparations, and it was my impression that little progress has been made in the treatment of leprosy.

I heard about John Early, the famous leper. John Early's home was originally in one of the Carolinas. He was educated in law, in addition to a sound general education, and developed a good command of the English language. He turned from law to religion and became a preacher of a radical type. At some time during his early years he was on military duty in the Philippines, and it is said that this is where he contracted his leprosy.

He was well known throughout the United States Public Health Service because of his many escapes from the colony. His most famous escapades consisted of trips to Washington, where he attempted to impress government officials with the need for changes at the leprosarium, which they had ignored when he attempted to handle matters by correspondence. It is said that he was paid great attention at one time when he registered at a prominent hotel in Washington and later announced that he was John Early, the famous leper.

Following one of his later escapes he made his way to California and acquired a house and a car, and recorded his ownership of them in such a manner that considerable provision had to be made for their disposal before he could be returned to the colony. I believe that a patient cannot be sent to Carville unless some satisfactory arrangements have been made for the disposal or care of his property.

Back in the hospital again he wrote an autobiography. Whatever the contents of the book, they were censored so much that not more than enough material for a single chapter remained. Undismayed, he tried to have it published under the title of *The Fourteenth Chapter in the Life of John Early, the Famous Leper.* I do not know whether it ever reached book form.

His last escape was made shortly before his death. This time he went back to his native Carolina hills. A doctor and an attendant from Carville were sent after him and, with the aid of several local peace officers, finally found John Early. However, no one would touch him except the two from Louisiana and it remained for them to drag him down the mountainside and back to the leprosarium. On his return, his sight and hearing failed rapidly and he died soon thereafter.

In the pathology laboratory there is a large glass specimen jar on which is a label headed "Treasury Department." In this container rest some of the remains of John Early. The many stories about this patient will probably keep his memory alive for a longer period of time than will the specimens in the jar bearing his name.

This long story has omitted many little incidents that occurred during my short visit, but to one who had seen only three cases of leprosy before, this experience was extremely interesting and instructive.

JOHN L. KEELEY, M.D.

NOTICES

MASSACHUSETTS MEMORIAL HOSPITALS

There will be a staff meeting of the Massachusetts Memorial Hospitals in the Evans Memorial Auditorium on Friday, February 28, at 8:15 p.m. Dr. C. W. Sewall will preside.

PROGRAM

Hypertension and/or the Albuminuria of Pregnancy. Dr. Foster Kellogg. Discussion by Dr. Duncan Reid.

Postnatal Care: A year's study in the Follow-Up Clinic. Drs. C. W. Sewall and O. C. Mullaney. Discussion by Dr. J. T. Williams.

NEW ENGLAND PATHOLOGICAL SOCIETY

The next meeting of the New England Pathological Society will be held on Thursday, February 20, at 8 p.m., at the Mallory Institute of Pathology, Boston City Hospital.

PROGRAM

Eosinophilic Granuloma of Bone. Dr. L. S. Jolliffe.

Intranuclear Inclusions in Infants. Dr. T. D. Kinney.

Intercapillary Glomerulosclerosis. Drs. H. Jeghers and O. J. Wollenman, Jr.

The Pathology of Athetosis: Is it malformation or birth injury? Dr. L. Alexander.

MASSACHUSETTS DEPARTMENT OF CIVIL SERVICE AND REGISTRATION

School Physician, Department of Health, Worcester, $1200 a Year

Director of State Civil Service, Ulysses J. Lupien, has recently announced that a competitive examination is to

be held on April 26 in order to find eligibles for appointment to the position of school physician, Department of Health, Worcester.

The entrance requirements are as follows: applicants who have not reached their thirtieth birthday on the day of examination will not be eligible to apply; applicants must be registered physicians under the State Board of Registration in Medicine. The subjects and weights of the examination are as follows: training and experience, 2; practical questions, 3; total, 5. Applicants must obtain a grade of 70 per cent in each subject in order to become eligible. The last date for filing applications is Saturday, April 12, at 12 o'clock noon.

NEW ENGLAND BRANCH OF THE AMERICAN UROLOGICAL ASSOCIATION

The ninety-first meeting of the New England Branch of the American Urological Association will be held at the Harvard Club of Boston, on Thursday, February 27, at 8:15 p.m.

PROGRAM

Recent Advancements with Chemotherapy in Infections of the Urinary Tract. Dr. E. N. Cook, of Rochester, Minnesota.

Chemotherapy in Gonococcal Infections. Dr. O. F. Cox.

Formal discussion to be opened by Drs. C. S. Keefer and Champ Lyons.

NORFOLK DISTRICT MEDICAL SOCIETY

A regular meeting of the Norfolk District Medical Society will be held at the Hotel Puritan, Boston, on Tuesday, February 25, at 8 p.m. Tel. KEN 1480.

PROGRAM

Business.

Medicolegal Meeting. Mr. Leland Powers and Dr. W. J. Brickley.

Discussion.

Collation.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

There will be a meeting of the New England Society of Physical Medicine at the Hotel Kenmore, Boston, on Wednesday, February 19, at 8:00 p.m. A business meeting at 6:00 p.m. will be followed by an informal dinner in the Empire Room at 6:30 p.m.

PROGRAM

Medical Preparedness. Dr. Walter G. Phippen, president, Massachusetts Medical Society.

All members of the medical profession are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, FEBRUARY 16

SUNDAY, FEBRUARY 16

†4 p.m. The Use and Abuse of Vitamins. Dr. Maurice B. Strauss. Free public lecture. Harvard Medical School, Building D.

†4 p.m. Our Food and Our Health. Mrs. Muriel L. Reese. Cambridge Hospital, Margaret Jewett Hall.

MONDAY, FEBRUARY 17

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

TUESDAY, FEBRUARY 18

*9–10 a.m. The Psychosomatic Problem: Its significance for the physician. Dr. Kurt Goldstein. Joseph H. Pratt Diagnostic Hospital.

*12 m. Chronic Arthritis. Dr. Frank R. Ober. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

WEDNESDAY, FEBRUARY 19

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

*2–4 p.m. Anemia. Drs. W. P. Murphy and Robert Zollinger. Peter Bent Brigham Hospital.

8 p.m. Boston Society of Biologists. Massachusetts Institute of Technology.

*8 p.m. Medical Preparedness. Dr. Walter G. Phippen. New England Society of Physical Medicine. Hotel Kenmore, Boston.

THURSDAY, FEBRUARY 20

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Children's Hospital.

*9–10 a.m. The Perennial Tonsil Problem. Dr. W. A. MacColl. Joseph H. Pratt Diagnostic Hospital.

8 p.m. New England Pathological Society. Boston City Hospital, Mallory Institute of Pathology.

FRIDAY, FEBRUARY 21

*9–10 a.m. Some Characteristics of Experimental Deficiency Diseases. Dr. O. A. Bessey. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

†Open to the public.

FEBRUARY 20–22 — American Orthopsychiatric Association, Inc. Page 999, issue of December 12.

FEBRUARY 24 — New England Heart Association. Page 262, issue of February 6.

FEBRUARY 27 — New England Branch of the American Urological Association. Notice above.

FEBRUARY 28 — Massachusetts Memorial Hospitals. Page 303.

MARCH 8 — American Board of Ophthalmology. Page 201, issue of August 1.

MARCH 12–14 — New England Hospital Assembly. Hotel Statler, Boston.

MARCH 13 — Pentucket Association of Physicians. Page 263, issue of August 15.

MARCH 21–22 — New York University College of Medicine, Alumni Day. Page 135, issue of January 16.

APRIL 21–25 — American College of Physicians. Page 1065, issue of June 20.

APRIL 28–30 — American Academy of Physical Medicine. Scientific session. Hotel Pennsylvania, New York City.

MAY 21, 22 — Massachusetts Medical Society, Boston.

MAY 28–JUNE 2 — American Board of Obstetrics and Gynecology. Page 262, issue of February 6.

JUNE 2–6 — American Medical Association. Cleveland, Ohio.

OCTOBER 14–17 — American Public Health Association. Page 135, issue of January 16.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH

MARCH 5 — X-ray in Heart Disease. Dr. Merrill C. Sosman. Essex Sanatorium, Middleton.

APRIL 2 — Pediatric Problems in General Practice. Dr. Joseph Garland. Addison Gilbert Hospital, Gloucester.

MAY 14 — Relation of the Doctor to the Law. Mr. Leland Powers. New Ocean House, Swampscott.

FRANKLIN

MARCH 11.

MAY 13.

Meetings will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

NORFOLK

FEBRUARY 25 — Notice above.

MARCH 25 — To be announced.

MAY 8 — Censors' meeting. Hotel Puritan.

SUFFOLK

APRIL 30 — Page 604, issue of October 10.

MAY 1 — Censors' meeting. Page 261, issue of February 6.

WORCESTER

MARCH 12 — Memorial Hospital, Worcester.

APRIL 9 — Hahnemann Hospital, Worcester.

Supper at 6:30 p.m. followed by a business meeting and scientific program.

BOOK REVIEWS

New Facts on Mental Disorders: Study of 89,190 cases. By Neil A. Dayton, M.D., M.C. 8°, cloth, 486 pp., with 110 graphs and 84 tables. Springfield, Illinois: Charles C Thomas, 1940. $4.50.

This book is a statistical study of the patients admitted to Massachusetts state mental hospitals during the years 1917 to 1933 inclusive. The collection of data on which the study is based was initiated by the late Dr. George M. Kline, commissioner of the Massachusetts Department of Mental Diseases, who secured a grant from the state legislature in 1926 for the purpose. The study extended over the ensuing period of eight years, with the aid of grants from the Laura E. Spellman Rockefeller Memorial Fund. The laborious task of organizing and analyzing the mass of data thus collected has been carried out since 1935 by Dr. Dayton with the help of an assistant and clerical workers and with the financial aid of the Rockefeller Foundation.

For the purposes of the study, the 89,190 cases that came under consideration were divided into four groups: 56,579 first admissions "with mental disorder"; 9299 first admissions "without mental disorder"; 20,635 readmissions "with mental disorder"; and 2677 readmissions "without mental disorder." After discussing the social and economic developments of the eventful years 1917 to 1933 (World War I, Prohibition, Depression) and considering possible influences on the number of persons admitted to mental hospitals in Massachusetts during those years, the author proceeds to the statistical analysis of the four groups of cases, with reference to age, nativity, alcoholism, marital status and clinical diagnosis. In the last chapter the author answers the question, "Are mental disorders on the increase?" as follows: "The larger part of the supposed increase in mental disorders has come about mechanically, through the extremely long hospital stay of patients with this type of illness. . . . Only one sixth of the total increase could be attributed to rising numbers of admissions."

It is impossible in a brief review to deal adequately with the numerous conclusions that emerge from the welter of data. A few of the highlights may be mentioned: "Mental disorder is a disease of old age," and "The highest proportion of newly developing cases of mental disorder (first admissions) do *not* occur in the younger or middle ages but in persons who have proved their adequacy by several decades of successful living." The foreign-born present the highest admission rates, and the native-born of native parentage the lowest. Chronic alcoholism is a prominent etiologic factor in one fifth of all admissions to mental hospitals in Massachusetts, and the evidence suggests that Prohibition may have been more successful, especially with women, in controlling alcoholism (even in the depression years) than has generally been realized; this suggestion may, however, be a reflection of decreased facilities for caring for alcoholic patients in the mental-hospital system. The author concludes that "the married have the least chance of developing mental disorders of any of the marital groups. The widowed, the single and the divorced, in order, show a higher incidence of mental disorders." An interesting detail is an apparent relation between religious denomination and the incidence of mental disorder: "Protestants present the highest admission rate . . . and are followed in order by the Catholics, other denominations and the Hebrews. The leading mental disorders in the Protestants are psychoses with Huntington's chorea and the senile psychoses, in the Catholics the alcoholic psychoses and psychoses with mental deficiency, and in the Hebrews the psychoneuroses and undiagnosed psychoses."

There is no doubt that this book is an extremely important and authoritative contribution to general psychiatric literature; it is certainly destined to become a standard reference that will be widely consulted and quoted for many years. Typographic features that deserve special mention are the many excellent graphs and the concise summaries at the beginning of each chapter.

Edinburgh Post-Graduate Lectures in Medicine. Vol I. 8°, cloth, 513 pp., with 110 figures, 32 tables and 11 charts. Edinburgh: Oliver and Boyd, 1940. 10s. 6d. ($2.10.)

This volume of lectures, delivered at the Royal Infirmary, Edinburgh, Scotland, is part of the postgraduate program organized over a generation ago in this great medical center. It is of timely interest to physicians in New England, where a similar program is now being intensively developed. With us, as in Great Britain, it has become recognized that "provision for postgraduate study is necessary if our profession is to maintain that high standard of efficiency upon which we pride ourselves," and that the physician must remain a student throughout his active professional life.

The thirty-three lectures comprising this book come from men who are authorities in their respective subjects, among them Edwin Bromwell, Sir David Wilkie and W. T. Ritchie. The range of subjects is wide and interesting, and particular emphasis is laid on their application to general practice. Several of the topics may be cited: "Upon the Pupil Reaction," "Some Modern Problems in Neurology," "Psychotherapy in General Practice," "Rational Use of Digitalis," "Proteins in the Treatment of Nephritis," "The Significance of Glycosuria," "The Acute Abdomen in Childhood," "The Lungs and Pleura — Certain Anatomical Facts in Relation to Disease," "Recent Development in the Surgery of Obstructive Jaundice, with Special Reference to the Risk of Hemorrhage."

In form and in content this book is worthy of the high Edinburgh tradition. It is labeled "Volume One." May it be followed by many more!

Clinical Heart Disease. By Samuel A. Levine, M.D. Second edition, revised and reset. 8°, cloth, 495 pp., with 109 illustrations. Philadelphia and London: W. B. Saunders Company, 1940. $6.00.

The second edition of this already well-known book follows in general the form and content of its predecessor. The presentation of the subject lends itself to easy reading and properly reflects the experience of the author as an investigator, a teacher and a specialist in the field of cardiovascular disease. A number of welcome additions and amplifications of practical importance appear in the new edition.

The book is designed and written primarily for the practicing physician. However, the special student of cardiovascular disease will encounter with interest many original ideas that have appeared in special publications in the past by the author and his associates, here to be reemphasized, modified, or abandoned in the light of further experience. For example, the operation of valvulotomy for mitral stenosis, proposed in 1923, has rightly been discarded as impracticable; the use of adrenalin administered subcutaneously as a "test" for angina pectoris in questionable cases, as the author points out, is fraught with danger; and the routine administration of quinidine sulfate following acute coronary thrombosis as a prophylactic

measure against fatal ventricular fibrillation has been modified in favor of its occasional use in special cases. With these recommendations there is general agreement. It is with mild disappointment, however, that one finds again in the new edition the suggestion that rheumatic infection may be the result of "some inherent hereditary defect in metabolism associated with growth or with the glands of internal secretion that renders some individuals particularly susceptible to some noxious agent that is fairly prevalent." To the reviewer, such speculation seems unduly fanciful. The discussion of angina pectoris and of coronary thrombosis is especially well arranged and should be most helpful in the management of patients with these disorders of the heart. Certain outstanding clinical problems are well emphasized in special chapters; for example, "Acute Cardiovascular Emergencies" and "The Clinical Significance of the Systolic Murmur." Furthermore, the newly added chapter, "Medicolegal Aspects of Heart Disease," will be especially welcome to the physician who, often against his desire, either on the witness stand or elsewhere finds himself faced with difficult decisions in connection with this aspect of heart disease.

The field of clinical electrocardiography is covered adequately, with well-chosen illustrations, in the final chapter of the book. Perhaps the rather gloomy outlook with which the author views the finding of evidence of intraventricular block, especially of the left-branch type, might have been tempered by the brief mention of so-called "functional-bundle-branch block" with a short PR interval—rare, to be sure, but important to be recognized.

The medical profession is fortunate in having available a new and up-to-date edition of this book, which is especially adapted to the needs of the practicing physician. Its continued usefulness is assured.

The Control of Tuberculosis in the United States. By Philip P. Jacobs, Ph.D. Revised edition. 8°, cloth, 387 pp. New York: National Tuberculosis Association, 1940. $2.00.

This book should prove useful to those interested in tuberculosis as well as to all who seek information concerning methods of preventive medicine.

The author was for many years associated with the educational and publicity program of the National Tuberculosis Association, and wrote extensively on health education. It is therefore fortunate that this work was completed before his untimely death.

The book deals with the history of the antituberculosis movement, and with methods for the control of tuberculosis in the United States. The subject matter is exhaustively treated, dealing with such varied topics as fund raising and case findings. There are excellent chapters entitled "Adult Health Education," "Social Service and Rehabilitation," "The Negro Problem," "Treatment and Hospitalization" and "Relations to the Medical Profession." The fundamental principles of the tuberculosis programs also receive attention.

The book reflects Mr. Jacobs's attitude as a crusader and enthusiastic teacher who understood in a practical way the psychology of health education under a democratic system. The style, although simple, is forceful, and the subject matter concisely but thoroughly treated. This book is the fruition of an active mind and scientific training in a chosen field.

All interested in disease-control programs will find valuable information in this work.

Gynecological and Obstetrical Pathology, with Clinical and Endocrine Relations. By Emil Novak, M.D., D.Sc. (Hon. Dublin). 8°, cloth, 496 pp., with 427 illustrations. Philadelphia: W. B. Saunders Company, 1940. $7.50.

This is an excellent book, presenting as it does the lesions of the female genital tract from the point of view of a gynecologist. It is easy to read and covers the subject very adequately. In addition there are excellent chapters on the normal physiology of the ovaries and pituitary gland, with their endocrine relations, and on the normal histologic changes in the endometrium in the course of the menstrual cycle. The pathologic states of each organ are grouped together in sections, and preceding each is a short description of the normal.

A major fault of the book is in the illustrations. The title page states proudly that there are four hundred and twenty-seven of them, but of these probably no more than a quarter are above criticism. This is because, in the first place, they were originally low-power photomicrographs, and, in the second, they seem to have been reduced in size in the printing. The result is a picture that lacks sufficient detail to mean much to anybody but an expert. It is also a very personal book, but what axe grinding there is does not intrude too much.

All in all, the average obstetrician and gynecologist should certainly have this book available for reference. Its use is greatly facilitated by a well-arranged twenty-three-page index.

Electrocardiography. By Chauncey C. Maher, M.D. and Paul H. Wosika, M.D. Third edition. 4°, cloth, 334 pp., with 42 diagrams and 5 radiograms. Baltimore: Williams and Wilkins Company, 1940. $4.00.

Electrocardiography has developed into another useful and important procedure for the clinician. Like the Wassermann test and x-ray examination, the electrocardiogram offers important data to be included or corroborated with the other clinical observations to arrive at an accurate diagnosis. The physician who observes the patient is the final judge in each case, even though the laboratory evidence may voice a dissenting opinion.

With this view in mind, the book is illuminating and practical. It gives the physician-student of medicine an opportunity to acquire a fundamental knowledge of electrocardiography. The one hundred electrocardiograms that are reproduced and discussed cover a goodly number of the common varieties of cardiac disease, including the arrhythmias, conduction deformities, axis deviations and changes that result from coronary occlusion. There are also a number of diagrams illustrating the intrinsic mechanism of the heart beat.

The arrangement of the book is in a convenient form, showing the electrocardiogram on one side of the page and its interpretation on the opposite one, preceded by a clinical diagnosis. The interpretations are clear, precise and conservative. This edition includes the fourth lead, the most notable recent addition to electrocardiography. The book is highly recommended.

Correction

The reviewer of *The Diagnosis and Treatment of Diseases of the Peripheral Arteries,* by Saul S. Samuels, wishes to correct an erroneous impression that may have been obtained from the review published in the issue of December 26, 1940. The opening sentence of the third paragraph of the review should have read, "Some of the subject matter in the book *appears to be misleading to the reviewer,*" inasmuch as in the reviewer's experience Uroselectan is an irritating solution for arteriography.